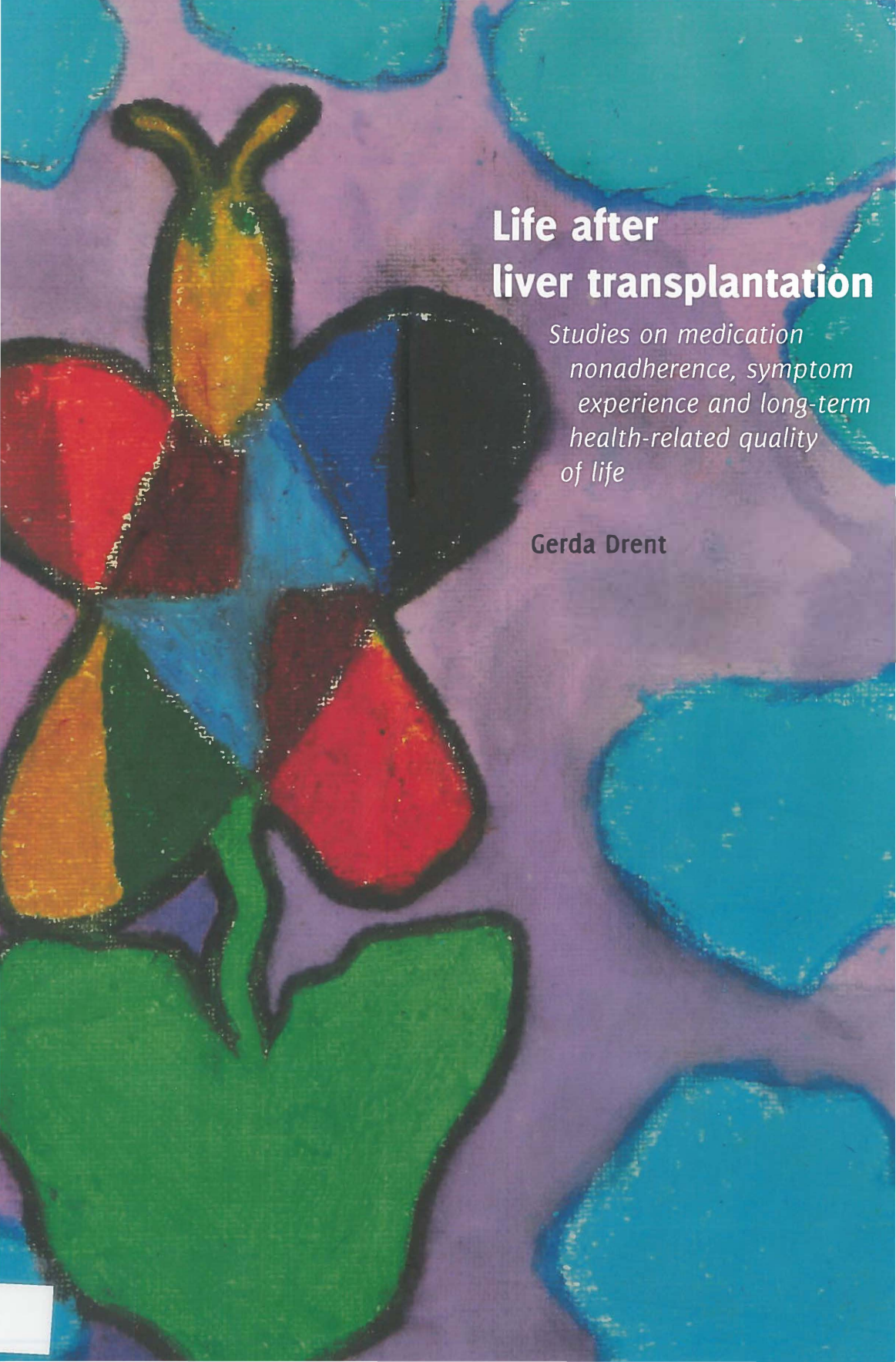

Life after liver transplantation

Studies on medication nonadherence, symptom experience and long-term health-related quality of life

Gerda Drent

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Stellingen

behorende bij het proefschrift

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1. Levertransplantatie brengt patiënten met eindstadium leverziekte geen genezing, maar is een behandelwijze met potentiële medische en psychosociale problemen (*dit proefschrift*).

2. Het vragen naar medicatietrouw moet onlosmakelijk verbonden zijn aan de behandeling (*dit proefschrift*).

3. Bijwerkingen van immuunsuppressie zoals deze door de patiënt worden ervaren verschillen in belangrijke mate van de bijwerkingen die door de behandelaars worden gecontroleerd (*dit proefschrift*).

4. De patiënt moet kunnen meebeslissen over het te volgen beleid t.a.v. immuunsuppressie na levertransplantatie (*dit proefschrift*).

5. De ernst van de lichamelijke beperkingen vanaf 15 jaar na levertransplantatie is geen maat voor kwaliteit van leven (*dit proefschrift*).

6. Therapieontrouw kan zeer functioneel zijn als het geen invloed heeft op het resultaat van de behandeling (*dit proefschrift*).

7. Het menszijn is de grootste risicofactor voor therapieontrouw (*Lars Osterberg*).

8. De Mexicaanse griep bezorgt meer hoofdbrekens dan griepverschijnselen.

9. Voorlichting over orgaandonatie moet beginnen in de bovenbouw van de basisschool.

10. Te weten wat men weet, en te weten wat men niet weet, dat is kennis (*Confucius*).

Drent, G
Life after liver transplantation. Studies on medication nonadherence, symptom experience and long-term health-related quality of life

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Studies on medication nonadherence, symptom experience and long-term health-related quality of life

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CONTENTS

CHAPTER 1

General introduction and outline of the thesis

LIVER TRANSPLANTATION

Orthotopic liver transplantation is a surgical procedure in which the diseased liver of a patient is replaced by a donor liver. The first liver transplant was performed in March 1963 in the USA by Thomas E. Starzl.[1] The University Medical Center of Groningen (UMCG) in the Netherlands started a liver transplant program for adults in 1979.[2] A program for transplantation in children followed in 1982. Until March 1th 2009 1066 liver transplantations in 867 adults and children have been performed at the UMCG.

The main indication for liver transplantation in adults is cirrhosis due to a variety of causes. Main indications at the UMCG, since 1996, were primary sclerosing cholangitis (18%), alcoholic cirrhosis (13%), hepatitis B cirrhosis (11%), hepatitis C cirrhosis (7%), primary biliary cirrhosis (9%), and acute liver failure (6%). Hepatocellular carcinoma was present in 11% of the recipients. A small minority of patients was transplanted for inborn errors of metabolism, e.g. primary hyperoxaluria (2%) and familial amyloidotic polyneuropathy (5%).[3]

Throughout the years the long-term survival prognosis after liver transplantation has gradually improved due to improvement of surgical techniques, better understanding of rejection and new immunosuppressive medications.[3-5] The patient survival rates at the UMCG for adult patients that were transplanted after 1996, are 86%, 78%, and 71%, at 1, 5 and 10 years after the procedure, respectively.[3] The European Liver Transplant Registry (ELTR) reports 1, 5, and 10 years patient survival rates of 82%, 70%, and 60 %, respectively, in adults that were transplanted since 1988.[6] Main causes of morbidity and mortality after liver transplantation are recurrence of liver disease, cardiovascular diseases, and malignancies. In part these complications can be ascribed to the use of immunosuppressive drugs.[5]

LIFE AFTER LIVER TRANSPLANTATION

The procedure of organ transplantation is strikingly described by Engle who discusses that "organ transplantation is not a cure for end-stage organ disease but an alternative form of treatment with both potential medical and psychosocial problems".[7] The effectiveness of the transplantation depends both on the skills of the health care team and on the lifelong, active co-operation of the patient.[8,9] Patients have to adhere strictly to lifelong immunosuppressive medication regardless of experienced side-effects. Infection control, self-monitoring (e.g. blood pressure and weight) and following a healthy life-style are expected skills of the patient in order to keep the complication rate as low as possible.[5,10,11]

Nowadays it is increasingly appreciated that it is important to incorporate the subjective experiences of the patients in the rating of the effectiveness of treatment and to understand the impact of it on the daily life and the quality of life of the patient.[12-14] Important interrelating issues in this respect are medication nonadherence, symptom experience, and health-related quality of life.

Medication nonadherence

Nonadherence (also called noncompliance) to medications can be intentional or non-intentional. When, for example, patients have a busy life-style, experience unpleasant side-effects of the medications, or are forgetful, they may forget to take their medications at the scheduled time or adapt the dose.[15,16] But nonadherence to medications that are prescribed to make a donor organ function as well as possible, whether it is intentional or non-intentional, may have very serious consequences for the patient.[17] Acute or chronic rejection can occur or, in the worst case, the organ can be lost. It is important to detect nonadherence before serious clinical consequences occur and to give the patient guidelines and support to manage their medication regimen according to best practice. Many studies on medication nonadherence in renal and heart transplant recipients have been conducted. These studies in renal and heart transplant patients showed that medication nonadherence was related to worse clinical outcome. So far, studies in liver transplant patients on this subject are scarce and conclusions are unclear.

Symptom experience

Many patients experience objective, but also subjective side-effects of medications.[18] Clinicians have always focused on objective side-effects as renal function impairment, osteoporosis, malignancies and more. But patients may also suffer from subjective perceived side-effects, as e.g. changed bodily appearance, sexual disorders and sleeplessness. These subjective side-effects can negatively influence health-related quality of life (HRQOL) and they can be a trigger for nonadherence with medications. Subjective side-effects have been a neglected area in clinical practice. It is unclear how the pattern of subjective side-effects is in adult liver transplant recipients and whether it affects nonadherence and HRQOL.

Health-related quality of life

Liver transplantation aims to improve HRQOL. Evidence from HRQOL-research can optimize the result of the liver transplantation. Full benefit and adequate support for the patient can be reached by thorough evaluation of threatened QOL-areas with special emphasis on long-term follow-up. As mentioned previously, immunosuppressive medications can cause health problems on the long-term and may influence HRQOL negatively. Many studies have been performed showing a good HRQOL short-term after liver transplantation.[19,20] But since liver transplantation already exists for three decades or more it would be interesting to know how transplant patients judge their HRQOL long-term after liver transplantation and whether they experience a lot of comorbidity due to the treatment.

OUTLINE OF THIS THESIS

The general aim of this thesis is to assess medication nonadherence, symptom experience, and long-term health-related quality of life in adult liver transplant recipients.

In **Chapter 2** an overview of the literature on subjective side-effects of immunosuppressive drugs, medication nonadherence and long-term health-related quality of life in adult liver transplant recipients is presented.

Chapters 3 to 5 concern investigations performed in a study group of 123 adult liver transplant recipients.

Chapter 3 reports on the study in which we prospectively assessed prednisolone nonadherence using electronic event monitoring (EEM) in an outpatient setting.

Chapter 4 explores the impact of prednisolone nonadherence, as measured with EEM, on clinical outcome during a two year follow-up.

Chapter 5 reports on the symptom experience associated with immunosuppressive drugs as assessed with the Modified Transplant Symptom Occurrence and Symptom Distress Scale. A possible relationship with medication nonadherence, as measured with EEM, is explored.

Chapters 6 and 7 concern investigations into the health status and long-term health-related quality of life in two well defined study groups.

In **Chapter 6** we studied the clinical outcome of adult patients surviving longer than 15 years after liver transplantation, with special interest for the broad range of comorbidity and the self-perceived quality of life.

Chapter 7 explores the quality of life of patients transplanted for familial amyloidotic polyneuropathy (FAP). FAP is an autosomal dominant disorder associated with mutations of the protein transthyretin, which is almost entirely produced in the liver. FAP characteristically presents with progressive peripheral and autonomic neuropathy, but cardiac amyloid is frequent and may dominate the clinical picture. Initially it was reported that liver transplantation resulted in overall improvement. However, it has become clear that in a substantial percentage of patients disease progression is not prevented in all organ systems. We were interested in the health-related quality of life in these patients after liver transplantation.

REFERENCES

1. Starzl TE, Groth CG, Brettschneider L, Penn I, Fulgniti VA, Moon JB, Blanchard H, Martin AJ jr., Porter KA. Orthotopic homotransplantation of the human liver. Ann Surg 1968;168:392-415.
2. Krom RA, Gips CH, Houthoff HJ, Newton D, Waaij vd D, Beelen J, Haagsma EB, Slooff MJH. Orthotopic liver transplantation in Groningen, The Netherlands (1979-1983). J Hepatol 1984;4:61s-65s.
3. Verdonk RC, Berg van den AP, Slooff MJH, Porte RJ, Haagsma EB. Liver transplantation: an update. Neth J Med 2007;65:372-80.
4. Bumgardner GL, Roberts JP. New Immunosuppressive agents. Gastroenterol Clin North Am 1993;22:421-49.
5. Benten D, Staufer K, Sterneck M. Orthotopic liver transplantation and what to do during follow-up: recommendations for the practitioner. Gastroenterol & Hepatol 2009;6:23-36.
6. European Liver Transplant Registry (ELTR), www.eltr.org, accessed march 27th 2009.
7. Engle D. Psychosocial aspects of the organ transplant experience: what has been established and what do we need for the future. J Clin Psychol 2001;57:521-49.
8. Chisholm MA. Issues of adherence to immunosuppressant therapy after solid-organ transplantation. Drugs 2002;62:567-75.
9. Morrissey PE, Flynn ML, Lin S. Medication noncompliance and its complications in transplant recipients. Drugs 2007;67:1463-81.
10. Bosscher DS, Drent G. De zorg voor patiënt en familie na transplantatie. Ned Tijdschrift Voor Intensive Care. Maart 1998;13:29-34.
11. Hellgren A, Berglund B, Gunnarsson U, Hansson K, Norberg U, Backmän L. Health-related quality of life after liver transplantation. Liver Transpl Surg 1998;4:215-21.
12. Goff JS, Glazner J, Bilir BM. Measuring outcome after liver transplantation: a critical review. Liver Transpl Surg 1998;4:189-96.
13. Acquardo C, Berzon R, Dubois D, Kline Leidy N, Marquis P, Revicki D, Rothman M. Incorporating the patient's perspective into drug development and communication: an ad hoc task force report of the patient-reported outcomes (PRO) harmonization group meeting at the Food and Drug Administration, February 16, 2001. Value Health 2003;6: 522-31.
14. Cleemput I, Dobbels F. Measuring patient-reported outcomes in solid organ transplant recipients. Pharmacoeconomics 2007;25:269-86.
15. De Geest S, Abraham I, Dunbar-Jacob J. Measuring transplant patients' compliance with immunosuppressive therapy. West J Nurs Res 1996;18:595-605.
16. Osterberg L, Blascke T. Adherence to medication. N Engl J Med 2005;353:487-97.
17. Fine RN, Becker Y, De Geest S, Eisen H, Ettenger R, Ewans R, Lapointe Rudow D, Mckay D, Neu A, Nevins T, Reyes J, Wray J, Dobbels F. Nonadherence consensus conference summary report. Am J Transpl 2009;9:35-41.
18. De Geest S, Moons P. The patient's appraisal of side-effects: the blind spot in quality-of-life assessments in transplant recipients. Nephrol Dial Transplant 2000;15:457-59.
19. Dew MA, Switzer GE, Goycoolea JM, Allen AS, Dimartini A, Kormos RL, Griffith BP. Does transplantation produce quality of life benefits? Transplantation 1997;64:1261-73.
20. Tome S, Wells JT, Said A, Lucey MR. Quality of life after liver transplantation. A systematic review. J Hepatol 2008;48:567-77.

CHAPTER 2

Symptom experience, nonadherence and quality of life in adult liver transplant recipients

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ABSTRACT

Survival outcomes after liver transplantation in adult patients have gradually improved with a five-year survival of about 70% and a ten-year survival of about 60%. The present review focuses on relevant patient-reported outcomes such as self-perceived side effects of immunosuppressive drugs, medication nonadherence and long-term health-related quality of life after liver transplantation. These entities are interrelated but were often studied separately.

Self-perceived symptom experience in liver transplant recipients has not been studied extensively. Symptoms that cause distress differ between men and women, e.g. symptoms related to cosmetic side effects of drugs.

Medication nonadherence seems to be infrequent, but if present may have serious consequences. Important risk factors were found to be the costs of drugs, age < 40 years, psychiatric disorders, side effects of drugs, beliefs that drugs were harmful, and large influence of the liver transplant on the patient's life.

Health-related quality of life is satisfactory, but below the level of the general population. Results, however, must be interpreted with caution as quality-of-life improvements may have been overstated due to variables such as selection bias (e.g. exclusion of severely ill and deceased patients), too many short-term studies, and suboptimal methodology.

Presently we lack data on the influence of recurrence of disease, "*de novo*" diseases and gender differences on health-related quality of life in liver transplanted patients.

INTRODUCTION

For several decades liver transplantation (LT) has been the accepted treatment for a gradually expanding variety of indications.[1,2] Life expectancy improved over time, due to better surgical techniques and preoperative and postoperative care,[1,3] with a five-year survival of about 70%, and a ten-year survival of about 60%.[2,4] An update on liver transplantation by Verdonk et al. was recently published in this journal.[1]

Formerly, the results of solid organ transplantation were mostly evaluated from the perspective of clinicians in terms of objective clinical outcomes, such as post-operative complications, renal impairment, hypertension, malignancies, osteoporosis, diabetes, and patient and graft survival. Nowadays, it is increasingly recognised that an evaluation of outcomes should incorporate the subjective experiences of the patients.[5]

The Food and Drug Administration in the USA strongly recommends that patient-reported outcomes (PRO) should be incorporated to evaluate the impact of treatment on patients' daily life and well-being. A patient-reported outcome can be defined as *"any outcome based on data provided by patients or by patient proxy as opposed to data provided from other sources"*.[5] Patient-reported outcomes may help to improve the quality of healthcare, and need to be taken into account when developing new drugs. PROs that are of importance to liver transplant patients are symptom experience, medication adherence and health-related quality of life.

The effectiveness of the treatment after solid organ transplantation depends both on the skills of the healthcare team and on the life-long, active cooperation of the patient.[6,7] Side effects as a consequence of taking of immunosuppressive medications, may occur. Assessment of side effects as it is perceived by the patients provides the transplant field with valuable information regarding the benefit and burden of immunosuppressive regimens.[8] A relationship has been found between symptom experience and nonadherence and health-related quality of life in heart, renal and lung transplant recipients.[9-23] The current review explores whether evidence supports these relationships in liver transplant patients.

Adherence (also called compliance or concordance) is defined as: 'the extent to which a person's behaviour – taking medication, following a diet, and/or executing lifestyle changes, corresponds with the *agreed* recommendations from a healthcare provider'.[24]

Nonadherence with the immunosuppressive regimen in solid organ transplant recipients is recognised as a major long-term problem with a negative impact on clinical outcome [25-30] and worse economic outcome.[31-34] The majority of research on adherence in transplantation, however, has been done in renal and heart transplantation. No reviews have been published on medication adherence in liver transplant patients specifically.

Health-related quality of life (HRQOL) is also recognized as an important patient-reported outcome. Solid organ transplantation remains a chronic condition which can have a high impact on the daily life and well-being of the patient.[35,36] For liver transplant patients specifically, health-related quality of life may well be influenced by long-term side effects of drugs, and by the status of the liver as "*de novo*" disease or recurrent disease may develop.[37-39]

The present review focuses on experience of symptoms related to side effects of immunosuppressive drugs, medication nonadherence and long-term health-related quality of life in adult liver transplant patients. The databases PubMed, PsychInfo, Cinahl, preCinahl, and the Cochrane Library, from 1966 to October 2008, were searched with the help of a medical librarian. A combination of following search terms was used: liver transplantation, liver transplant*, compliance, non(-)compliance, non(-)adherence, adherence, concordance, symptom experience, symptom frequency, symptom distress, subjective side effects, subjective adverse effects, quality of life, general health status, long-term. Further selection criteria were English language publications and focusing on adult patients. Excluded were articles that focused on living donation. The articles found on all of the topics were screened and in addition to this search strategy the references of the publications were searched for additional publications. In total we found 41 publications on the three subjects: six studies on symptom experience, 14 studies with the main focus on medication nonadherence and 21 studies on long-term HRQOL. From the 21 studies on long-term HRQOL five studies that were published after the latest meta-analysis were selected for this review.

SYMPTOM EXPERIENCE

Symptom experience is a critical post-transplant outcome and it provides the transplant field with valuable information regarding the benefit and burden of immunosuppressive regimens as it is perceived by the patients.[8] Symptom experience refers to the patient's subjective experience of side effects related to immunosuppressive drugs and it can be divided in perceived symptom occurrence (cognitive part of symptom experience) and perceived symptom distress (emotional part of symptom experience).[8-12] Symptom occurrence is described along the dimensions of frequency, duration and severity of perceived side effects of immunosuppressive medications. Symptom distress, expressing the emotional burden related to side effects, demonstrates how patients are affected in daily life by these symptoms.[5] Many clinical symptoms may not be perceived by the patients as very distressing, and also the level of distress may differ in patients.[20] For instance, the patients may worry more about skin alterations, sexual disorders, depressive symptoms and stomach complaints than about hypertension or renal impairment. The amount of perceived distress was found to be related to health-related quality of life and to nonadherence in heart, renal and lung transplant recipients,[9-23] Kidney transplant recipients with a higher level of symptom occurrence and symptom distress for instance had a higher rate of nonadherence.[19] More 'drug holidays' as a measure of nonadherence and a higher level of symptom occurrence and distress was related to a worse quality of life in lung transplant recipients.[23] It is important to find evidence about symptom experience in liver transplant patients for three reasons: (1) health care workers must be informed that symptom occurrence and/or a higher level of perceived distress may worsen patient's well-being and that it may lead to nonadherence, (2) it can be used to educate the patient and his/her

relatives about the side effects of immunosuppressive medications and (3) it can be used in developing new drugs and in prescribing existing immunosuppressive medications based on patients' preferences.[20,40] Only a few studies were retrieved that report on symptom experience after liver transplantation.[40-45] Foley *et al.*[41] report a low score on occurrence of symptom frequency and perceived distress in 26 liver transplant recipients. Most frequently reported symptoms were fatigue, bodily appearance, excessive hair growth and overeating. However the sample was rather small and the response rate was only 59%. Karam *et al.* assessed 'Measures of Disease', more specific physically symptoms and severity of symptom distress, in 126 liver, 229 renal and 113 heart transplant recipients as part of long-term Quality-of life-assessment. [44] 'The Measures of Disease' reported by the transplant patients were significantly worse than in the general population, with the worst score for renal transplant patients. The symptom distress score for psychological symptoms revealed that renal transplant recipients had a worse HRQOL than liver transplant recipients. However, limited specifications about the symptoms were provided.

We assessed symptom experience in 108 adult liver transplant patients[40] with the 29-item Modified Transplant Symptom Occurrence and Symptom Distress Scale [9,10,46] and found that increased hair growth was the most frequent symptom in male and female recipients.

The most distressing symptom in women was excessive and/or painful periods, while in men this was impotence. Male and females did not differ with respect to symptom frequency, but overall symptom distress was more serious in women than in men. It was also shown that the most frequently reported symptoms do not necessarily cause the most perceived distress. Stomach, back and muscle complaints were listed in the Top Ten of most distressing symptoms for both sexes. Dividing the sample in a cohort with a short-term (1-4 years)- and a long-term (5-18 years) follow-up, clear differences over time and between genders were noted. Women in the long-term cohort reported more cosmetic side effects. A decrease in symptom frequency and symptom distress was not seen in the long-term cohort. This might be explained by the fact that comorbidity from long-term immunosuppression increases through the years and by the effect of ageing, but this needs further investigation in future studies. No relationship was found between symptom experience and prednisolone nonadherence as measured with electronic monitoring.[47]

Drawing firm conclusions from these few studies on symptom experience, however, is difficult, because the studies used different measurement instruments, and the symptoms assessed were not always described in detail. Symptoms that cause distress may differ between men and women. Furthermore, no conclusions can be drawn about the relationship with different immunosuppressive regimens, nor about the relationship with medication adherence and HRQOL.

NONADHERENCE WITH IMMUNOSUPPRESSIVE MEDICATION

Patients' adherence to immunosuppressive medications plays a key role in obtaining and maintaining a good clinical outcome. Fourteen studies on nonadherence in adult patients after liver transplantation were retrieved.[14,15,25,28,47-56] Most of the studies that were published before 2000 included only small numbers of patients.

Measurement of nonadherence

Measurement of medication nonadherence can be divided into direct and indirect methods.[57] Direct methods are: direct observation or measurement of a drug (metabolite) in blood or urine. Indirect methods are patient self-report, collateral report, pill counts, rates of prescription refills, assessment of clinical outcome, electronic medication monitors (EM), and measurement of physiological markers (i.e. heart rate of patients taking beta-blockers).[57-60]

Adherence measurement methods in adult liver transplant adherence studies have been: monitoring blood levels of calcineurin inhibitors [15,20,25,48-51], self report [15,51-54], collateral report[25], retrospective chart review[14,51,55], clinical outcome [25,28,49,51,55,56], electronic monitoring (EM)[47] and appointment nonadherence.[51] The diagnostic accuracy of each method has been discussed extensively by several authors.[57,59-62] Recent research findings using cross validation and diagnostic research, suggest that a combination of several measurement methods has higher sensitivity compare to using a single method. [57,62]

Establishing nonadherence in clinical practice

In clinical practice a simple measure to establish suspected nonadherence, e.g. a patient is not responding to therapy, is by just asking the patient at a scheduled follow-up how often he/she could not take the medication as prescribed in the last four weeks and what caused this omission.[57] Another useful method is to contact the patient's pharmacy about refilling prescriptions[57] or to ask the patient to bring the medication along to a scheduled appointment with the physician or clinical nurse specialist.

Prevalence of nonadherence

As the retrieved studies use different methodology it is not easy to derive a general nonadherence prevalence rate. Schweizer *et al.*[15] reported the first prospective adherence study (n=13) among adult liver transplant recipients. Nonadherence was suspected when unexplained decreases in cyclosporine blood levels were observed. Three of 13 liver transplant recipients were found to be nonadherent. In a retrospective study among 118 patients who had undergone liver transplantation for alcoholic liver cirrhosis, Berlakovich *et al.*[28] reported that 19 recipients (16%) were not within the target range of whole blood trough-levels of the calcineurin-inhibitor. This, however, in itself does not prove nonadherence. We have studied prednisolone nonadherence with the use of electronic monitoring and found an overall high level of dosing

adherence for prednisolone (median of 99%), except that timing adherence, which describes 'the percentage of days that opening of the bottle was within three hours of the subject's chosen time of day to routinely take their prednisolone dose', was low in about one-third of the patients.[47] Dew *et al.*[63] analyzed adherence after solid organ transplantation, and included seven liver transplant studies on medication nonadherence in her meta-analysis. Liver transplant recipients had a medication nonadherence rate of 6.7 cases per 100 patients per year (PPY) *vs* 15 cases per 100 PPY in heart transplant recipients and 36 cases per 100 PPY in renal transplant recipients. The limited available evidence suggests that adherence for medication intake after liver transplantation seems to be good, and more favourable than in other transplant recipients. Nonadherence should of course also be evaluated in view of its possible clinical consequences of medication nonadherence.

Clinical consequences of nonadherence

Medication nonadherence must have a measurable effect on the clinical outcome for it to be clinically relevant.[64] The ultimate goal is to develop a clinically relevant definition of nonadherence indicating the level of nonadherence that is connected with increased risk for poor clinical outcome. Review of nonadherence studies in renal transplant recipients revealed that nonadherence was associated with poor clinical outcome, e.g. rejection episodes and graft loss.[29,65] Research in heart transplant populations[27] with electronic monitoring showed that minor deviations from the dosing schedule were associated with increased risks of late acute rejection, graft loss, and mortality.

In a retrospective review by Mor *et al.*[25] in 375 liver transplant patients it was found that nonadherence accounted for 34,6% of late acute rejection episodes. In a retrospective study among 118 patients who had undergone liver transplantation for alcoholic liver cirrhosis, Berlakovich *et al.*[28] reported that late acute rejection differed significantly between the adherent patients (5% with acute rejection) and the nonadherent patients (22% with acute rejection). In our study concerning prednisolone nonadherence, we looked for a relationship between nonadherence and clinical outcomes during a 2-year follow-up including liver tests, acute rejection episodes, changes in dosages of immunosuppression, hospital re-admissions, and patient and graft survival.[56] Except for a somewhat higher alkaline phosphatase in patients who were less adherent, no relationship between prednisolone nonadherence and clinical outcome parameters was found.[56] It is possible, however, that the level of nonadherence in our patient population was too low to be of clinical significance. O'Carroll *et al.*[51] conducted a retrospective audit in 435 Scottish patients who were beyond one year after LT. Approximately one out of 100 patients died from poor adherence and nonadherence may have played a role in development of chronic rejection.

These studies show on the one hand that medication nonadherence may have serious consequences for graft and patient survival. On the other hand the level of nonadherence must be substantial with abstinence of medication probably for many weeks.

Economic consequences of nonadherence

Nonadherence with the immunosuppressive regimen has found to be associated with poor economic outcome, but has not been studied in adult liver transplant patients thus far.[31-33] Economic consequences, using data from the renal transplant literature, include higher healthcare costs among nonadherent patients in comparison with adherent patients in terms of hospital care, retransplantation, ambulatory care, nursing homes, productivity loss and 'out-of-pocket' expenses of patients and relatives.[31-33] On the other hand, when lifetime costs of adherent versus nonadherent renal transplant patients were compared, Cleemput *et al.*[33] found lower costs in nonadherent patients over lifetime, due to a shorter life span in nonadherent patients (i.e. a median survival of 12 *vs* 16 years). Yet quality adjusted life years (QALYs) were higher in adherent patients.[33]

Risk factors for nonadherence

Knowing that nonadherence can have a negative impact on outcomes after transplantation, clinicians should be aware of possible risk factors for nonadherence so that adequate interventions can be undertaken. Reported risk factors in liver transplant patients are higher costs of medications[15], age< 40 years[47], psychiatric disorders[14,15], side effects of medications[14,15,51], beliefs that medications were harmful[51], and experiencing a large effect of the transplant on the patients' daily life.[51] More studies are needed to judge the influence of higher level factors related to the healthcare centre and healthcare providers. For example in a multi-centre study of renal transplant patients using electronic monitoring, associations were found between the transplant centre and adherence.[66] Another study showed that nonadherence rates were higher in the United States compared with Europe, and highlight that healthcare system factors, such as insurance coverage, are possibly an influencing factor of higher nonadherence rates in the USA.[7,63,67-69]

Interventions

No intervention studies to enhance medication adherence in adult liver transplant patients, have been published to our knowledge. As nonadherence is a complex behaviour, usually not predictable and individual to every patient it is difficult to develop effective strategies to enhance adherence.[7,70] Several reviews about interventions in other chronic illness patient populations have been published.[71-74] One conclusion they have in common is that no 'magic bullet' was found and that very few effective interventions significantly affected clinical outcomes in the long term. Patient education is important and may include discharge teaching and introducing a self-medication programme.[57,70] Once-daily medication dosing and simplifying dosing so that it fits into the lifestyle of the patient may improve adherence.[34,57,71,74] Of further importance are investment in a good relationship between the healthcare professionals and the patient, with more frequent interactions with attention to adherence.[57,71,74] Additionally, this includes means of easy communication by phone or e-mail and broadening opening hours of the out-patient clinic to shorten waiting times.[57] Interventions need to be tailored to the individual patient. A combination of

educational, behavioural and affective interventions seems to be most effective, but they are complex and labour-intensive.[71,74]

LONG-TERM HEALTH-RELATED QUALITY OF LIFE

The World Health Organization defined Health as *"a state of complete physical, mental and social well-being and not merely the absence of disease"*.[75] General HRQOL improves significantly from pre- to post-LT but most findings refer to a relatively short duration of follow-up.[37-39]

Long-term results indicate that HRQOL, after the initial improvement from pre- to post-LT, remains rather stable through the years and is not always negatively influenced by comorbidity and clinical side effects of medications.[37-39] Results show, however, that LT patients have significant deficiencies in most QOL areas when they are compared with healthy controls.[40] The impact of etiology of liver diseases on HRQOL, such as alcoholic liver disease, HCV infection, acute liver failure, remains inconclusive with contradicting findings of HRQOL gains. The assumption was made by Tome *et al.*[39] that recurrence of disease, e.g. Hepatitis C, and development of *"de novo"* diseases, e.g. diabetes mellitus, after LT might be of higher influence on a worsened HRQOL than the original etiology of the disease.[39] In view of sexual functioning and employment more recent studies show that females tend to have a lower HRQOL compared with males. Sexual health was found to be unchanged after LT compared with the period before LT when data of longitudinal studies were combined. Employment rates varied considerably after transplantation.[39] Unemployment was predicted by age, longer duration of disability before LT, unskilled workers, lower income, and unemployment status.[39] Five new publications, one qualitative and four quantitative studies, assessing long-term HRQOL have been published since the most recent meta-analysis of Tome *et al.*[36,39,76-79] Median follow-up ranged from 4,4 years to more than 15 years after LT. The main findings of these studies are that varying levels of physical and psychosocial disability may persist for many years after LT, although patients describe having productive and meaningful lives with a positive outlook despite remaining uncertainty about the future.[36] Physical impairment led to significantly lower employment[76] but did not have an impact on satisfaction and self-care.[77] Long-term HRQOL did not seem to be related to the level of clinically observed comorbidity[77] or to the use of calcineurin inhibiting drugs.[78] Job rehabilitation in the first year after LT had a positive influence on long-term HRQOL.[78] Age above 60 years, female gender and post-transplant complications as recurrent disease and osteoporosis were associated with poorer physical functioning.[79]

These new studies also report a lower HRQOL than in the general population. In three of the four quantitative studies the SF-36[80] was used as a generic instrument to measure HRQOL[76,78,79] and one study also used a disease specific questionnaire.[79]

In summary, so far recent HRQOL studies add evidence in that QOL remains satisfactory in the long-term after LT, but lower compared with that of the general population. Although some of the recent studies on long-term HRQOL contribute

to earlier assumptions that overall long-term HRQOL does not seem to be affected by the level of comorbidity and that female patients experience a worse HRQOL compared with men, more studies on long-term HRQOL after LT are needed to gain more understanding.

CONCLUSIONS

The present review focused on three important patient reported outcomes in adult liver transplant patients, i.e. perceived subjective side effects of immunosuppressive drugs (i.e. symptom experience), medication nonadherence and long-term health-related quality of life. Clearly, these entities are interrelated but were often studied separately.

We found that self-reported symptom experience in liver transplant recipients has not been studied extensively. Differences between different immunosuppressive regimens were not explored so far in this respect. Also the relationship between symptom experience and medication adherence and HRQOL needs further study. Special attention should be paid to the level of perceived symptom distress and its impact on the daily life of the patient as a high level of distress might lead to nonadherence and worse HRQOL, as experienced in kidney, heart and lung transplant patients.

Medication nonadherence as measured to date seems to be infrequent, but if present may have serious consequences. Important risk factors included, age< 40 years, and side effects of medications.[15,47,51] More studies are needed to gain more insight into clinically relevant nonadherence and to judge the influence of the healthcare centre and health care-providers. More studies into the prevalence of medication nonadherence and corresponding risk factors are needed before appropriate intervention studies can be developed. Evidence from studies in chronically ill patients and other organ transplant patients show us that there is not one single effective intervention available and that a combination of multidimensional and multi-level interventions may be effective for long-term results to enhance adherence.[71,74] This is an important area for future research, yet the clinical consequences of nonadherence in liver transplant patients should also determine if this is a priority.

Results show that long-term HRQOL is satisfactory, but it is below the level of the general population. These results must be interpreted with caution as HRQOL benefits after liver transplantation may have been overstated due to variables such as selection bias (e.g. exclusion of severely ill and deceased patients), too many short term studies, and suboptimal methodology.[39] In addition, HRQOL will also be affected by cultural, economic and social factors which are difficult to incorporate in research.[38,39,81] In studying HRQOL from the perspective of patient-reported outcomes it is recommended to use both a disease-specific questionnaire and a generic questionnaire. The former detects disease-specific changes and the latter allows comparison of results with other groups of patients with chronic diseases. Presently we lack data on the influence of recurrence of disease and of "*de novo*" diseases in adult liver transplant patients. Also gender differences should be given more attention.

RECOMMENDATIONS

In conclusion two main recommendations can be made. Firstly it is important that assessment of adherence is an integrated part of the treatment plan of the patient, and poor adherence should always be considered when a patient is not responding to therapy.[57] Secondly, physicians should be aware of the possible influence of subjective side effects of immunosuppressive medications on medication adherence and of the impact of corresponding distress on the daily life of the patient. In the future, medication regimens should not only be based on clinical data alone, but, when possible, also on subjective patient-reported outcomes.

REFERENCES

1. Verdonk RC, Berg van den AP, Slooff MJH, et al. Liver transplantation: an update. Neth J Med 2007; 65:372-80.
2. European LiverTransplant Registry, www.eltr.org, accessed October 27th 2008.
3. Cleemput I, Dobbels F. Measuring patient-reported outcomes in solid organ transplant recipients. Pharmacoec 2007;25:269-86.
4. Schiffman ML, Saab S, Feng S, Abecassis MI, et al. Liver and intestine transplantation in the United States, 1995-2004. Am J Transpl 2006;6(Part 2):1170-87.
5. Acquardo C, Berzon R, Dubois D, et al. Incorporating the patient's perspective into drug development and communication: an ad hoc task force report of the patient-reported outcomes (PRO) harmonization group meeting at the Food and Drug Administration, February 16, 2001. Value Health 2003;6: 522-31.
6. Morrissey PE, Flynn ML, Lin S. Medication non-compliance and its implications in transplant recipients. Drugs 2007;67:1463-81.
7. Chisholm MA. Issues of adherence to immunosuppressant therapy after solid-organ transplantation. Drugs 2002;62:567-75.
8. Dobbels F, Moons P, Abraham I, et al. Measuring symptom experience of side effects of immunosuppressive drugs: the Modified Transplant Symptom Occurrence and Distress Scale. Transpl Int 2008;21:764-73.
9. Lough M, Lindsey A, Shinn J, Stotts N. Life satisfaction following heart transplantation. J Heart Transpl 1985;4:446-49.
10. Lough ME, Lindsey AM, Shinn JA, Stotts NA. Impact of symptom frequency and symptom distress on self-reported quality of life in heart transplant recipients. Heart & Lung 1987;16:193-200.
11. Moons P, De Geest S, Abraham I, et al. Symptom experience associated with maintenance immunosuppression after heart transplantation: Patients' appraisal of side effects. Heart & Lung 1998;27:315-25.
12. Moons P, Fairchild S, De Geest S. Patients' appraisal of side effects in quality of life assessments of immunosuppressive regimens. In: Cochat P, et al. Eds. Immunosuppression under Trial. London: Kluwer Academic Publishers, 1999, 69.
13. Didlake RH, Dreyfus K, Kerman RH, et al. Patient noncompliance: a major cause of late graft failure in cyclosporine-treated renal transplants. Transpl Proc 1988; XX:63-69.
14. Rovelli M, Palmeri D, Vossler E, et al. Noncompliance in organ transplant recipients. Transplant Proc 1989;21:833-34.
15. Schweizer RT, Rovelli M, Palmeri D, et al. Noncompliance in organ transplant recipients. Transplantation 1990;49:374-77.
16. Swanson MA, Palmeri D, Vossler E, et al.. Noncompliance in organ transplant recipients. Pharmacotherapy 1991;11:173S-74S.
17. Sketris I, Grobler M, West M, et al. Factors affecting adherence with cyclosporine in adult renal transplant recipients. Transplant Proc 1994;26: 2538.
18. Moons P, Vanrenterghem Y, Hooff van JP, et al. Health-related quality of life and symptom experience in tacrolimus-based regimens after renal transplantation: a multicentre study. Transpl Int 2003;16: 653-64 .
19. Texeira De Barros C, Cabrita J. Self-report of symptom frequency and symptom distress in kidney transplant recipients. Pharmacoepidemiol Drug Saf 1999;8:395-403.
20. De Geest, Moons P. The patient's appraisal of side effects: the blind spot in quality of life assessments in transplant recipients. Nephrol Dial Transpl 2000;15:457-59.
21. Rosenberger J, Geckova AM, van Dijk JP, et al. Prevalence and characteristics of noncompliant behaviour and its risk factors in kidney transplant recipients. Transpl Int 2005;18:1072-8.
22. Takemoto SK, Pinsky BW, Schnitzler MA, et al. A retrospective analysis of immunosuppression compliance, dose reduction and discontinuation in kidney transplant recipients. Am J Transpl 2007;7:2704-11.

23. Kugler C, Fischer S, Gottlieb J, et al. Symptom experience after lung transplantation: impact on quality of life and adherence. Clin Tanspl 2007;21:590-96.
24. World Health Organization. Adherence to long-term therapies. Evidence for action. Section 1, Geneva, Switzerland 2003:17-19.
25. Mor E, Gonwa Th A, Husberg BS, et al. Late-onset acute rejection in orthotopic liver transplantation – associated risk factors and outcome. Transplantation 1992;54:821-24.
26. De Geest S, Borgermans L, Gemoets H, et al. Incidence, determinants, and consequences of subclinical noncompliance with immunosuppressive therapy in renal transplant recipients. Transplantation 1995;59:340-47.
27. De Geest S, Abraham I, Moons Ph, et al. Late acute rejection and subclinical noncompliance with cyclosporine therapy in heart transplant recipients. J of Heart Lung Transplant 1998;17:854-63.
28. Berlakovich GA, Langer F, Freundorfer E, et al. General compliance after liver transplantation for alcoholic cirrhosis. Transpl Int 2000;13:129-35.
29. Denhaerynck K, Dobbels F, Cleemput, I, et al. Prevalence, consequences, and determinants of nonadherence in adult renal transplant patients: a literature review. Transpl Int 200 5; 18:1121-33.
30. Morrissey PE, Reinert S, Yango A, et al. Factors contributing to acute rejection in renal transplantation: the role of noncompliance. Transpl Proc 2005;37:2044-47.
31. Loghman-Adham M. Medication non-compliance in patients with chronic disease: Issues in dialysis and renal transplantation. Am J Manag Care 2003;9:155-71.
32. Cleemput I, Kesteloot K, De Geest S. A review of the literature on the economics of noncompliance. Room for methodological improvement. Health Policy 2002;59:65-94.
33. Cleemput, I, Kesteloot K, Vanrenterghem Y, De Geest S. The economic implications of non-adherence after renal transplantation. Pharmacoec 2004;22:1217-34.
34. Hansen R, Seifeldin R, Noe L. Medication adherence in chronic disease: issues in posttransplant immunosuppression. Transpl Proc 2007;39:1287-1300.
35. De Geest S, Dobbels F, Fluri C, et al. Adherence to the therapeutic regimen in heart, lung, and heart-lung transplant recipients. J Card Nurs 2005;20:588-98.
36. Dudley T, Chaplin D, Clifford C, et al. Quality of life after liver transplantation for hepatitis C infection. Qual Life Res 2007;16:1299-1308.
37. Dew MA, Switzer GE, Goycoolea JM, et al. Does transplantation produce quality of life benefits? Transplantation 1997;64:1261-73.
38. Bravata DM, Olkin I, Barnato AE, et al. Health-related quality of life after liver transplantation: A meta-analysis. LiverTranspl Surg 1999;5:318-31.
39. Tome S, Wells JT, Said A, Lucey MR. Quality of life after liver transplantation. A systematic review. J Hepatol 2008;48:567-77.
40. Drent G, Moons P, De Geest S, et al. Symptom experience associated with immunosuppressive drugs after liver transplantation: possible relationship with medication non-compliance? Clin Transpl 2008;22:700-9.
41. Foley TC, Davis CP, Gonway PA. Liver transplant recipients-self report of symptom frequency, symptom distress, quality of life. Transpl Proc 1989;21:2417.
42. Levy MF, Jennings L, Abouljoud MS, et al. Quality of life improvements at one, two, and five years after liver transplantation. Transplantation 1995;59:515-18.
43. Cowling T, Jennings LW, Jung GS, et al. Comparing quality of life following liver transplantation for Laennec's versus non-Laennec's patients. Clin Transpl 2000;14:115-20.
44. Karam VH, Gasquet I, Delvart V, et al. Quality of life in adult survivors beyond 10 years after liver, kidney, and heart transplantation. Transplantation 2003;76:1699-1704.
45. Cowling T, Jennings LW, Goldstein RM, et al. Liver Transplantation and health-related quality of life: scoring differences between men and women. LiverTranspl 2004;10:88-96.
46. Moons P, De Geest S, Versteven K, et al. Psychometric properties of the Modified Transplant Symptom Occurrence and Symptom Distress Scale. J Nurs Meas 2001; 9:115-34.
47. Drent G, Haagsma EB, De Geest S, van den Berg AP, Ten Vergert EM, Van den Bosch HJ, Slooff MJH, Kleibeuker JH. Prevalence of prednisolone (non)compliance in adult liver transplant recipients. Transpl Int 2005;18:960-66.

48. Howard L, Fahy T, Wong P, et al. Psychiatric outcome in alcoholic liver transplant patients. Q J Med 1994;87:731-36.
49. Berlakovich GA, Steininger R, Herbst F, et al. Efficacy of liver transplantation for alcoholic cirrhosis with respect to recidivism and compliance. Transplantation 1994;58:560-65.
50. Fábrega E, Crespo J, Casafont F, et al. Alcohol recidivism after liver transplantation for alcoholic cirrhosis. J Clin Gastroenterol 1998;26:204-6.
51. O'Carroll RE, McGregor LM, Swanson V, et al. Adherence to medication after liver transplantation in Scotland: a pilot study. Liver Transpl 2006;12:1862-68.
52. Beresford TP, Schwartz J, Wilson D, et al. The short-term psychological health of alcoholic and non-alcoholic liver transplant recipients. Alcohol Clin Exp Res 1992;16:996-1000.
53. Osorio RW, Ascher NL, Avery M, et al. Predicting recidivism after orthotopic liver transplantation for alcoholic liver disease. Hepatology 1994;20:105-10.
54. Everson G, Bharadhwaj G, House R, et al. Long-term follow-up of patients with alcoholic liver disease who underwent hepatic transplantation. Liver Transpl Surg 1997;3:263-74.
55. Rabkin JM, La Melena de V, Orloff SL, et al. Late mortality after orthotopic liver transplantation. Am J Surg 2001;181:475-79.
56. Drent G, De Geest S, Haagsma EB. Prednisolone noncompliance and outcome in liver transplant recipients. Letter to the editor. Transpl Int 2006;19:342-43.
57. Osterberg L, Blascke T. Adherence to medication. N Engl J Med 2005;353:487-97.
58. Gordis L. Conceptual and methodological problems in measuring patient compliance. In: Meichenbaum D, Turk DC (eds): Facilitating Treatment Adherence. New York, Plenum Press; 1987:23-45.
59. Cramer JA. Overview of methods to measure and enhance patient compliance. In: Cramer JA, Spilker B (eds.): Patient Compliance in Medical Practice and clinical trials. New York, Raven Press; 1991:31-10.
60. De Geest S, Abraham I, Dunbar-Jacob: Measuring transplant patients' compliance with immunosuppressive therapy. West J Nurs Res 1996;18:595-605.
61. Denhaerynck K, Schäfer-Keller P, Young J, et al. Examining assumptions regarding valid electronic monitoring of medication therapy: development of a validation framework and its application on a European sample of kidney transplant recipients. BMC Med Res Meth 2008;8:5. Available from: www.biomedcentral.com.
62. Schäfer-Keller P, Steiger J, Bock A, et al. Diagnostic accuracy of measurement methods to assess non-adherence to immunosuppressive drugs in kidney transplantation. Am J Transpl 2008;8:616-26.
63. Dew MA, DiMartini AF, De Vito Dabbs A, et al. Rates and risk factors for nonadherence to the medical regimen after adult solid organ transplantation. Transplantation 2007;83:858-73.
64. Chapman JR. Compliance: The patient, the doctor, and the medication? Transplantation 2004;77:782-86.
65. Butler JA, Peveler RC, Roderick P, Horne R, Mason JC. Measuring compliance with drug regimens after renal transplantation: comparison of self-report and clinician rating with electronic monitoring. Transplantation 2004;77:786-89.
66. Weng FL, Israni AK, Joffe MM, et al. Race and electronically measured adherence to immunosuppressive medications after deceased donor renal transplantation. J Am Soc Nephrol 2005;16:1839-48.
67. Paris W, Dunham S, Sebastian A, et al. Medication nonadherence and its relation to financial restriction. J Transpl Coord 1999;9:149-52.
68. Denhaerynck K, Desmyttere A, Dobbels F, et al. Nonadherence with immunosuppressive drugs: U.S. compared with European kidney transplant recipients. Prog Transplant 2006;206-14.
69. Friedman AL, Geoghegan SR, Noelle M, et al. Medication errors in the outpatient setting. Classification and root cause analysis. Arg Surg 2007;142:278-83.
70. Schäfer-Keller P, Lyon S, Van-Gelder F, et al. A practical approach to promoting adherence to immunosuppressive medication after renal transplantation. Curr Op Nephrol Hypert 2006;15(Clinical update 2):S1-S6.

71. Roter DL, Hall JA, Merisca R, et al. Effectiveness of interventions to improve patient compliance: a meta-analysis. Med Care 1998;36:1138-61.
72. Peterson AM, Takiya L, Finley R. Meta-analysis of trials and interventions to improve medication adherence. Am J Health-Syst-Pharm 2003;60:657-65.
73. Kripalani S, Yao X, Haynes B. Interventions to enhance medication adherence in chronic medical conditions. Arch Intern Med 2007;167:540-50.
74. Haynes RB, Ackloo E, Sahota N, et al. Interventions for enhancing medication adherence (Review). The Cochrane Database of Systematic Reviews 2008, Issue 2.
75. Constitution of the World Health Organization. Geneva. Basic documents, Forty-Fifth edition, Supplement October 2006.
76. Saab S, Wiese C, Ibrahim AB,et al. Employment and quality of life in liver transplant recipients. Liver Transpl 2007; 13:1330-38.
77. Kroon de LA, Drent G, Berg van den AP, et al. Current health status of patients who have survived more than 15 years after liver transplantation. Neth J Med, 2007, Jul-Aug; 65(7):252-8.
78. Kousoulas L, Neipp M, Barg-Hock H,et al. Health-related quality of life in adult transplant recipients more than 15 years after orthotopic liver transplantation. Transpl Int 2008; 21: 1052-58.
79. Desai R, Jamieson NV, Gimson AE, et al. Quality of life up to 30 years following liver transplantation. LiverTranspl 2008;14:1473-79.
80. Ware J, Snow KK, Kosinski M, Gandek B. SF-36 Health Survey, Manual and Interpretation Guide. Boston: The Health Institute, New England Medical Center, 1993.
81. Goff JS, Glazner J, Bilir BM. Measuring outcome after liver transplantation: a critical review. Liver Transpl Surg 1998;4:189-96.

CHAPTER 3

Prevalence of prednisolone (non)compliance in adult liver transplant recipients

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ABSTRACT

Limited evidence is available concerning (non) compliance with the immunosuppressive regimen in adult liver transplant recipients. In our study we prospectively assessed prednisolone (non) compliance in 108 adult liver transplant recipients using electronic event monitoring (EEM) in an outpatient setting. The EEM is a pill bottle fitted with a cap containing a microelectronic circuit that registers date and time of bottle openings and closings. Median taking compliance was 100% (range 60 -105%), median dosing compliance was 99% (range 58-100%), median timing compliance (TIC) was 94% (42-100%). A drug holiday (DH) of ≥ 48 hours was found in 39% of the patients; of ≥72 hours in 16% of the patients. Using EEM in liver transplant recipients, we found an overall high level of compliance for prednisolone, except that TIC was low in about one third of the patients. Age below 40 years was found a significant risk factor for decreased TIC and for DHs of ≥ 48 hours.

INTRODUCTION

Compliance, can be defined as "the extent to which a person's behaviour - taking medications, following a diet and/or executing lifestyle changes - corresponds with agreed recommendations from a health care provider"[1]. The effectiveness of any treatment does not only depend on the right choice of therapy, but also on the active co-operation of the patient in the therapeutic regimen[2]. If prescribed drugs are crucial for maintaining vital physiological functions, then the medical and economic consequences of variable compliance can be large[3]. It has been reported that noncompliance with immunosuppressive drugs after kidney or heart transplantation can lead to rejection [4-7], causing graft loss or even death [8].The presence of noncompliance after heart transplantation has been shown to relate to increased numbers of readmission's and higher total medical costs [9]. Research on compliance with immunosuppressive medication in adult liver transplant recipients is limited. Medication noncompliance as detected by unexplained low levels of cyclosporine has been found in 8 – 23% of patients [4,7,8,10,11]. Medication noncompliance based on self-report was found to be 3% [11]. One study reported an increase of episodes with late acute rejection in the noncompliant patient group [4].

In studying noncompliance two approaches can be identified [5]. In the first approach, 'clinical' noncompliance is assessed in relation to the occurrence of a clinical event such as a rejection episode, graft loss, or death. For example, in a retrospective review of 375 liver transplant patients (post transplant status longer than 6 months) Mor et al [4] showed that noncompliance was a major cause of late acute rejection. A total of 31 episodes in 26 patients were identified: 18 episodes were associated with subtherapeutic cyclosporine blood levels; 7 of these episodes were due to noncompliance. The second approach focuses on subclinical noncompliance, i.e. situations not yet accompanied by,, but potentially leading to a clinical event. The first approach includes only the tip of the proverbial iceberg and captures only a small proportion of the actual noncompliers. In contrast, the second focuses on the iceberg as a whole as it enables us to detect all noncompliant patients regardless of their present clinical status [5]. In the present study we are interested in the second approach in order to detect all patients showing medication noncompliance after liver transplantation regardless of their clinical status.

A 'gold standard' for measurement of medication (non) compliance does not exist [12]. The methods for compliance assessment in liver transplantation so far have been: review of patients records [13], questionnaire [11], patient interviews [8], and monitoring blood levels of calcineurin inhibitors [4,7,8,10,13]. These methods have their specific limitations [14-18]. A technologically advanced and more sophisticated method for the measurement of (non)compliance is the use of electronic devices [14,15,19]. Electronic event monitoring (EEM) refers to a pill bottle fitted with a cap containing a microelectronic circuit [14,15]. Date and time of opening of the bottle by removal of the cap is electronically registered. With EEM, frequency of over- or under-dosing, and trends in noncompliance during week or month are registered [14,18]. The data registered also allows detecting patterns of noncompliant behavior [15]. Despite the fact

that electronic monitoring does not actually prove ingestion of a pill [20] it has shown to be the most sensitive measure of medication compliance research to date [18,21]. Experience with the use of EEM showed that it is highly improbable that pills are consistently removed from the bottle without being ingested by the patient over a monitoring period of approximately 90 days [21].
The aim of the present study was to assess the prevalence of prednisolone (non) compliance using EEM methodology in adult liver transplant recipients on outpatient setting. In addition, the possible relation between several variables, such as age and complexity of overall medication, was studied in order to find risk factors for noncompliant behaviour.

MATERIALS AND METHODS

All adult patients with a follow-up of at least 1 year after liver transplantation were eligible for the present study. The study was approved by the Medical Ethical Committee of the University Hospital of Groningen. Inclusion criteria were the use of 10 mg of prednisolone once daily as part of the immunosuppressive regimen, stable clinical situation in out-of-hospital setting, literacy (Dutch language), and written informed consent. The patients were invited to participate during their protocolled yearly control after liver transplantation and were subsequently enrolled. From the medical records data were collected concerning date of transplantation, gender, age, primary liver disease, complexity of the medication regimen (immunosuppressive and other drugs) in terms of number of pills per 24 hours, number of medications and number of administrations, and body mass index (BMI).
The EEM: compliance with prednisolone therapy was assessed using the Medication Event Monitoring System (Aardex® Ltd., Zug, Switzerland). The EEM consists of a pill bottle fitted with a cap containing a microelectronic circuit registering the date and time of bottle opening and closings. Openings of the bottle are recorded as presumptive doses. Stored data are downloaded to a personal computer for further analysis. Data are presented in calendar plots and a chronology. For an example see Figure 1.
The following compliance definitions with electronic monitoring were used in this study: Taking compliance (TC) describes the percentage of bottle openings compared with the total number of doses (openings) prescribed. For example, overcompliance can be registered in this way. Dosing compliance (DC) describes the percentage of days on which the patient has correctly opened the bottle as prescribed (in our study once daily). A day was defined to begin at 03:00:00 a.m local time and ending at the following day at 02:59:59 a.m. Patients who took their one-day dose after midnight but before 3:00 a.m. were not rated as noncompliant based on this definition of a day. Timing compliance (TIC) describes the percentage of days that opening of the bottle was within 3 hours of the subject's chosen time of day to routinely take their prednisolone dose. A drug holiday (DH) was defined as no medication intake (bottle opening) during 48 h or more (DH-48) or during 72 h or more (3 consecutive days) (DH-72).

For the present study the content of the EEM-medication bottle was prepared by the Pharmacy of the University Hospital Groningen and filled with 150 capsules of 10-mg prednisolone per bottle. This amount of capsules was amply sufficient for a measurement period of 4 months.
Study patients received verbal and written information about how to use the EEM-medication bottle and when to return the bottle. They were told that the cap 'registered' the intake of the prednisolone capsule. The patients were instructed to use the EEM-medication bottle for a 4-month period and take one capsule a day. After this period the bottle could be returned by mail free of charge.
Compliance with EEM-guidelines was determined at the completion of the study period (once the EEM-medication bottle was returned) by means of an interview by telephone.

Statistical analysis

Data were checked for normality. Descriptive statistics and frequencies were calculated for relevant parameters. Spearman correlation and Mann Whitney *U* were used where appropriate. A *P*-value below or equal to 0.05 was considered to indicate statistical significance. All data were analysed using SPSS 11.5 (SPSS Inc., Chicago, IL, USA).

RESULTS

Study group

Initially 123 patients fulfilled the inclusion criteria and started with EEM. However, one patient stopped EEM at the very beginning of the measurement period due to a change of prednisolone dose. The exclusion interview by telephone at the completion of the study revealed that 12 patients had violated the EEM-guidelines. The reasons were as follows. Four patients explained that they were afraid to forget their pills because they were used to a medication box. They returned to their own medication routine. Six patients admitted to take the prednisolone capsule out of the EEM-medication bottle in the evening but swallowed the capsule in the morning. And 2 patients did not independently manage their medication as they had partners who took completely care of the medication regimen. In addition the data of the EEM-caps of 2 patients could not be retrieved. Thus, after exclusion of these 15 patients, the study group consisted of 108 patients with a median age of 47 years (range 22-71); 66 were female. Patient characteristics are listed in Table 1.
The major etiological causes of primary liver disease were primary biliary cirrhosis (19%) and primary sclerosing cholangitis (22%). The median follow-up after liver transplantation was 4 years (range 1-18). The medication regimen consisted of median 10 pills (range 4-24) and median six different drugs (range 1-11) distributed over median 3 medication administrations per 24 h (range 1-9). The maintenance immunosuppressive regimen consisted of prednisolone + azathioprine + cyclosporine in 57% of the patients. Overweight (BMI over 25 kg/m^2) was found in 54% of the liver transplant recipients.

Table 1. Patient characteristics (n=108)

Patient characteristics (n=108)	
Gender (male/female) (n)	42/66 (39%/61%)
Age (years)	47 (22-71)
Primary liver disease (n)	
Primary biliary cirrhosis	20 (19%)
Primary sclerosing cholangitis	24 (22%)
Auto-immune hepatitis	16 (15%)
Cryptogenic liver cirrhosis	12 (11%)
Alcoholic liver cirrhosis	7 (6%)
Other	29 (27%)
Years after transplant	4 (1 -18)
Medication complexity	
Number pills/24 hours	10 (4-24)
Number of medications	6 (1-11)
Number of administrations	3 (1-9)
Immunosuppressive regimen (n)	
Pred/aza/cya*	61 (56%)
Pred/aza	39 (36%)
Pred/cya	7 (7%)
Pred/tacrolimus	1 (1%)
Body Mass Index	25 (18-45)
% Overweight†	54%

**pred, prednisolone; aza, azathioprine; cya, cyclosporine*
† Overweight: Body Mass Index › 25 kg/m2

Prevalence of prednisolone (non)compliance

Results are shown in Table 2 and Figures 1-3.
The TC was high with a median of 100% (range 60-105%). Twenty of the 108 patients (19%) took more prednisolone than prescribed which resulted in overcompliance. In 4 patients (4%) TC was below 90%, the lowest being 60% (see Fig. 2).
Median DC was 99% (range 58-100%). Forty-four patients (41%) never forgot to take one capsule each day (DC 100%). In 7 of the 108 patients (6%) DC was below 90%, the lowest being 58% (see Fig. 2).
The TIC showed large variations as can be seen in Table 2. The median TIC was 94% (range 42-100%). Only 13 of the 108 patients (12 %) managed to take the capsule always about the same time of the day (TIC 100%). In 37 patients (34 %) TIC was below 90%, and in 15 patients (14%) below 75% (see Fig. 2).
A DH of 48 h or more (DH-48) during the 4 months EEM monitoring was seen in 42 of the 108 patients (39%) with a median of 2 DH-48 's (range 1-14) per patient. The

Table 2. Prevalence of prednisolone noncompliance (%)

Compliance	Lowest	P10	P25	P50	P75	P90	Highest
Taking compliance (TC)	60	94	98	100	100	101	105
Dosing compliance (DC)	58	92	97	99	100	100	100
Timing compliance (TIC)	42	67	87	94	98	100	100

P = percentile

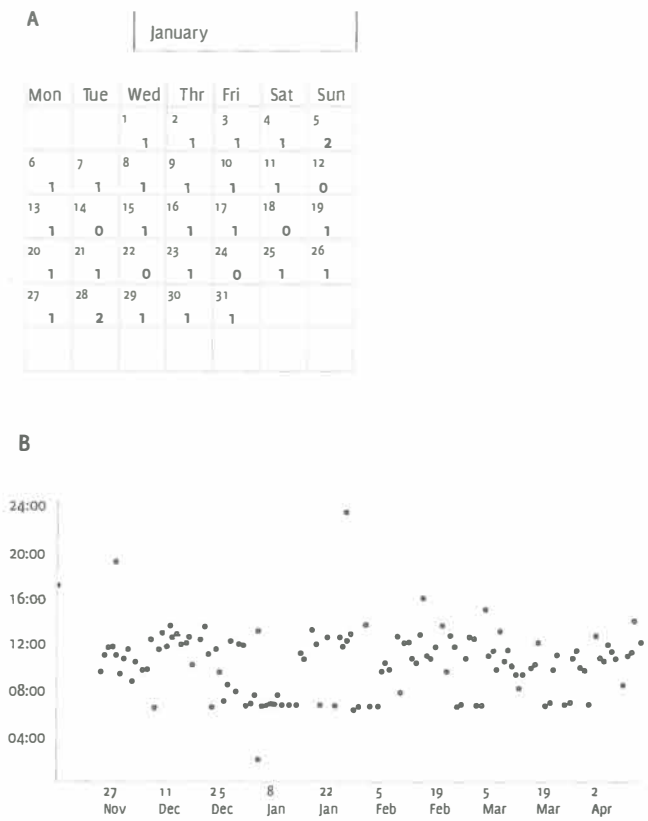

Figure 1. Calender plot (A) and chronology (B) of a study participant with poor compliance. Prescribed regimen is one capsule of 10 mg prednisolone per day at a fixed time.

median duration was 51 h (range 48-192). A drug holiday of 72 hours or more (DH-72) was seen in 17 of the 108 patients (16%). The number of DH-72 's was median one per patient (range 1-10). The duration was median 105 h (range 72-192).

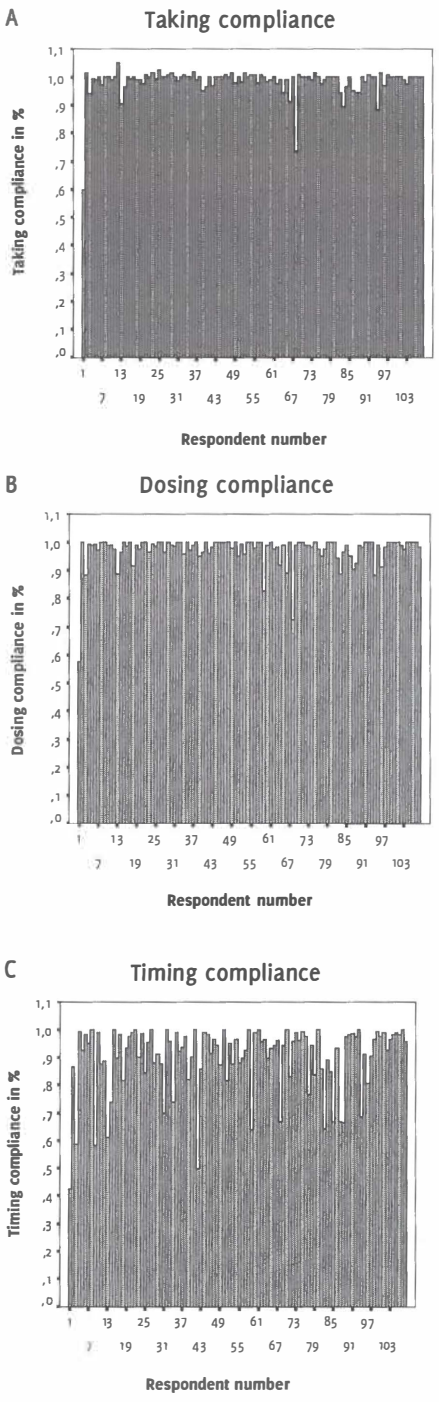

Figure 2. Bar plots of Taking Compliance, Dosing Compliance, and Timing Compliance, respectively; n = 108 patients.

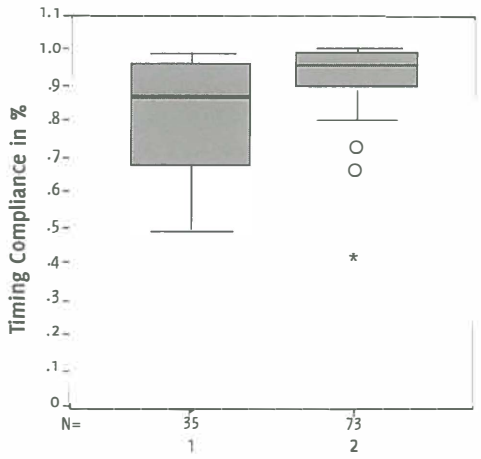

Figure 3. Boxplot of relation between Timing Compliance and Age; n = 108 patients; p<0.001

* extreme outlier.

Relations between the (non)compliance parameters and patient characteristics

Significant correlations were found between TC, DC, TIC, and DH ($p<0.01$). On the individual level however a low TIC did sometimes concur with a high TC or DC.
With respect to the parameters listed in Table 1, a significant correlation was found between TIC and age ($p<0.01$) and between age and DHs of 48 h or more ($p<0.05$). Patients above 40 years of age showed a significantly ($p<0.001$) better TIC compared to patients younger than 40 years (Fig. 3). They also had significantly ($p<0.05$) less DHs of 48 h or more.

DISCUSSION

Using EEM methodology we found an overall high level of compliance for prednisolone, except that TIC was lower in a substantial number of patients, which related to younger age of the patients. Younger age was also related to a higher amount of DHs of 48 h or more. Research on compliance with immunosuppressive medication and causes of noncompliance in adult liver transplant recipients is limited. The majority of studies focusing on compliance issues in liver transplantation studied alcohol recidivism [7,10,11,22,23]. A few studies report on medication compliance, with use of different methods.
Schweizer *et al.* [8] reported the first compliance study among adult liver transplant recipients. It was a prospective study in 13 patients. Patient records were reviewed concerning appointment noncompliance and medication noncompliance. Medication noncompliance was suspected when unexplained decreases in cyclosporine blood levels were observed. Three of 13 (23%) of the liver transplant patients were found

to be noncompliant and 2 of these patients died. Mental disease and alcoholism were identified as determinants of medication and/or appointment noncompliance. Berlakovich *et al.*[10] found that 7.8% of the cyclosporine blood levels of a sample of 44 liver transplant recipients were not within target limits, suggesting subclinical noncompliance with immunosuppressive therapy. In a later retrospective study [7] among 118 patients who had undergone OLT for alcoholic liver cirrhosis drug compliance was one of the subjects investigated. Cyclosporine or tacrolimus blood levels of 19 recipients (16%) were not within the target range. Late acute rejection defined as 'any biopsy-proven acute rejection episode after 3 months following transplantation and requiring rescue therapy', differed significantly between the compliant (5%) and the noncompliant (21%) group. Osorio *et al.* [11] compared medication noncompliance of 37 patients transplanted for alcoholic liver cirrhosis with a control group of 37 patients transplanted for other reasons using the method of self-report. Noncompliance with medication was found to be 3% in both groups. In a retrospective review of 375 patients (post-transplant status longer than 6 months) Mor *et al.* [4] showed that noncompliance was a major cause of late acute rejection. A total of 31 episodes in 26 patients were identified: 18 episodes were associated with subtherapeutic cyclosporine blood levels; 7 of these episodes were due to noncompliance. Noncompliance with the immunosuppressive regimen was documented by directly confronting the patient or families with the issue of noncompliance.

Our study differs from these studies by the use of EEM methodology which enabled us to study the whole spectrum of compliance in a group of patients not primarily suspected of noncompliance as judged by abnormal liver tests or unexplained low drug levels. The use of cyclosporine or tacrolimus blood levels can be challenged as a reliable measure of noncompliance with immunosuppressive regimen[15,17,18]. Although a drug assay is a direct measure of medication ingestion, results only prove medication intake over the past few days as the half-life of the calcineurin inhibitors prevents extrapolation of results to a longer time interval[15,17,18] . We also did not choose to study a special subgroup of patients like alcoholics. Yet, some comments on our patient group need to be made. First, by choosing 10 mg prednisolone as pill in the EEM-bottle, patients on lower prednisolone dosages, and patients without prednisolone were excluded. As mainly patients transplanted before the 90s, and patients with originally auto-immune diseases use prednisolone as part of their immunosuppressive regimen, our study group counted mainly patients with previous primary biliary cirrhosis, primary sclerosing cholangitis, and autoimmune hepatitis, and lacked patients with viral disease (often former drug addicts) and contained only a small number of patients with alcoholic liver disease (Table 1). Second, by asking for literacy and Dutch language a substantial number of patients from ethnic minorities were excluded. However, although it is our experience that these groups (former alcoholic or drug addicts, patients from an ethnic minority) in general need more attention in order to comply to rules, there are insufficient data that have shown them to be consistently less compliant. Nevertheless, we should be careful to extrapolate our findings to these groups.

We found high taking and DC in our liver transplant group, median 100 % and 99.2% respectively. These figures are much higher than those reported in several non-transplant patient groups with other drugs, also investigated with use of EEM. For example a TC of 66% is reported for migraine prophylaxis [24], 74% for isosorbid dinitrate [25], 76% for doxycycline [26], 81 % in HIV-infected adults [27], 83% for long-term drug treatment in chronic disease [20], 86% for multiple anti-epileptic medications [28]. Interestingly the figures reported in renal and heart transplant recipients are closer to our liver transplant recipients. In 19 adolescent renal transplant recipients, measured for cyclosporine compliance, a TC of 91% (range 64 - 100%) was reported [29]. In heart transplant recipients [6,16] measured for cyclosporine compliance, TC was 99% (range 84-100%) and DC 99% (range 71-100%). In comparison with the heart transplant recipients the range of compliance was broader in our patients. It might be concluded that in general organ transplant recipients are quite good compliant but best compliant are heart transplant recipients, which seems understandable given the function of the organs.

Most worrisome was the TIC in our patient group. In 34% of patients TIC was below 90%, in 14% below 75%. The heart transplant study mentioned above [6,16] has shown the importance of taking cyclosporine at regular times of the day. It was found that occasionally taking evening doses of cyclosporine after midnight or a median variation of dosing intervals of more than 2 h and 50 min is associated with an increased risk for late acute rejection episodes. In general it is known that recommended intervals of medication intake are set in the interest of maintaining action above some minimum level [19]. When a scheduled dose is delayed it can cause subtherapeutic drug concentrations. On the contrary when a scheduled dose is taken too soon it can cause higher drug concentrations and thereby unwanted side effects.

The consequences of variable TIC with prednisolone remain unclear and need to be further substantiated.

TIC and DH-48 in our study were found to relate to age, in that younger patients were less compliant and took more DHs. Younger age as a risk factor for noncompliance has also been found in other studies [27,30]. In a study among HIV-infected adults, patients older than 50 years demonstrated significantly better medication adherence than younger patients (88% vs 78%) [27]. A relation between age and compliance was not present in the study in heart transplant recipients [16], probably because compliance was overall high and because these patients were overall older (median age 56 years) than our liver transplant patients (median 47 years).

If optimal compliance is considered to be at the level of 100%, an important issue is at what level noncompliance becomes clinically relevant. Our feeling is that compliance above 90% is satisfactory, but this can be questioned. Clinically relevant parameters to be investigated prospectively in this respect are related to outcome of the liver, side effects of drugs (overcompliance), costs and number of admissions etc. Also the importance of TIC versus DC needs further study. Further study is also needed on determinants of noncompliance, besides age, especially psychosocial factors.

The present prospective study of noncompliance is considered a first step in a process to discover pretransplant determinants of noncompliance and subsequently to study

the effects of pre and post-transplant interventions (for example specific education for younger patients) on noncompliance and outcome after liver transplantation. The results of the present study already imply that an intervention study will require a much larger number of patients than the present study.
In conclusion, using EEM methodology in liver transplant recipients, we found a seemingly good overall compliance for prednisolone, except that TIC was low in about one third of the patients. Age below 40 years was found a significant risk factor for decreased TIC and for a higher amount of DHs of 48 h or more. Further study is needed to determine the consequences and psychosocial determinants of less than optimal compliance, after which an intervention study can be designed.

Acknowledgements
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REFERENCES

1. World Health Organization. Adherence to long-term therapies. Evidence for action. Section 1. Switzerland, 2003; 17-19.
2. Bunzel B, Laederach-Hofmann K. Solid organ transplantation: Are there predictors for posttransplant noncompliance? A literature overview. Transplantation 2000;70:711-716.
3. Urquhart J, Patient non-compliance with drug regimens: measurement, clinical correlates, economic impact. Eur Heart J 1996; 17 (Suppl.A):8-15.
4. Mor E, Gonwa Th A, Husberg B S, Goldstein RM, Klintmalm GB. Late-onset acute rejection in orthotopic liver transplantation - associated risk factors and outcome. Transplantation 1992; 54:821-824.
5. De Geest S, Borgermans L, Gemoets H, Abraham I, Vanhaecke H, Evers G, et al. Incidence, determinants, and consequences of subclinical noncompliance with immunosuppressive therapy in renal transplant recipients. Transplantation 1995; 59:340-347.
6. De Geest S, Abraham I, Moons Ph, Vandeputte M, Van Cleemput J, Evers G ,et al. Late acute rejection and subclinical noncompliance with cyclosporine therapy in heart transplant recipients. J of Heart Lung Transplant. 1998;17:854-863.
7. Berlakovich GA, Langer F, Freundorfer E, Windhager Th, Rockenschaub S, Sporn E, et al. General compliance after liver transplantation for alcoholic cirrhosis. Transpl Int 2000;13:129-135.
8. Schweizer RT, Rovelli M, Palmeri D, Vossler E, Hull D, Bartus S. Noncompliance in organ transplant recipients. Transplantation 1990; 49:374-377.
9. Paris W, Muchmore J, Pribil A, Zuhdi N, Cooper DK. Study of the relative incidences of psychosocial factors before and after heart transplantation and the influence of posttransplantation psychosocial factors on heart transplantation outcome. J Heart Lung Transplant 1994;13:424-430.
10. Berlakovich GA, Steininger R, Herbst F, Barlan M, Mittlböck M, Mühlbacher F. Efficacy of liver transplantation for alcoholic cirrhosis with respect to recidivism and compliance. Transplantation 1994;58:560-565.
11. Osorio RW, Ascher NL, Avery M, Bachetti P, Roberts JP, and Lake JR. Prediciting recidivism after orthotopic liver transplantation for alcoholic liver disease. Hepatology 1994;20:105-110.
12. Cramer JA, Mattson RH, Prevey ML, Scheyer RD, Ouelette VL. How often is medication taken as prescribed? A novel assessment technique. JAMA 1989;261:3273-3277.
13. Rovelli M, Palmeri D, Vossler E, Bartus S, Hull D, Schweizer RT. Noncompliance in organ transplant recipients. Transplant Proc 1989;21:833-834.
14. Cramer JA. Overview of methods to measure and enhance patient compliance. In: Cramer JA and

Spilker B, eds. Patient compliance in medical practice and clinical trials. 1 ed. New York: Raven Press; 1991: 3-10.
15. De Geest S, Abraham I, Dunbar-Jacob J. Measuring transplant patients' compliance with immunosuppressive therapy. West J Nurs Res 1996;18:595-605.
16. De Geest S. Subclinical noncompliance with immunosuppressive therapy in heart transplant recipients; A cluster analytic study. Doctoral Dissertation. Katholieke Universiteit Leuven; Faculty Of Medicine; School of Public Health; 1996.
17. Gordis L. Conceptual and methodological problems in measuring patient compliance. In: Meichenbaum D and Turk DC, eds. Facilitating treatment adherence. 1 ed. New York: Plenum Press; 1987: 23-45.
18. Spilker B. Methods of assessing and improving patient compliance in clinical trials. In: Cramer JA. and Spilker B, eds. Patient compliance in medical practice and clinical trials. 1 ed. New York: Raven Press; 1991: 37-56.
19. Urquhart J, De Klerk E. Contending paradigms for the interpretation of data on patient compliance with therapeutic drug regimens. Stat Med 1998; 17:251-267.
20. Kruse W, Weber E. Dynamics of drug regimen compliance - Its assessment by microprocessor-based monitoring. Eur J Clin Pharmacol 1990; 38:561-565.
21. Kastrissios H, Blaschke TF. Medication compliance as a feature in drug development. Annu Rev Pharmacol Toxicol 1997; 37:451-475.
22. Gish RG, Lee AH, Keffe EB, Rome H, Concepcion W, Esquivel CO. Liver transplantation for patients with alcoholism and end-stage liver disease. Am J of Gastroenterolog 1993; 88:1337-1342.
23. Howard L, Fahy T. Liver transplantation for alcoholic liver disease. B J Psych 1997;171:497-500.
24. Mulleners WM, Whitmarsch TE., Steiner TJ. Noncompliance may render migraine prophylaxis useless, but once-daily regimens are better. Chephalagia 1998;18:52-56.
25. Straka RJ, Fish JT, Benson SR, Suh J Th. Patient self-reporting of compliance does not correspond with electronic monitoring: an evaluation using isosorbide dinitrate as a model drug. Pharmacotherapy 1997;17:126-132.
26. Augenbraun M, Bachmann L, Wallace T, Dubouchet L, McCormack W, Hook E W. Compliance with doxycycline therapy in sexually transmitted diseases clinics. Sex Transm Dis 1998; 25:1-4.
27. Hinkin CH, Hardy DJ, Mason KI, Castellon SA, Durvasula RS, Lam MN, Stefaniak M. Medication adherence in HIV-infected adults: Effect of patients age, cognitive status, and substance abuse. AIDS 2004;18 (Suppl 1):S19-S25.
28. Cramer J, Vachon L, Desforges C, Sussman NM. Dose frequency and dose interval compliance with multiple antiepileptic medications during a controlled clinical trial. Epilepsia 1995;36:1111-1117.
29. Blowey DL, Hébert D, Arbus GS, Pool R, Korus M, Koren G. Compliance with cyclosporine in adolescent renal transplant recipients. Ped Nephrol 1997;11:547-551.
30. Rianthavorn P, Ettenger RB, Malekzadeh M, Marik JL, Struber M. Noncompliance with immunosuppressive medications in pediatric and adolescent patients receiving solid-organ transplants. Transplantation 2004;77:778-782.

CHAPTER

4

Prednisolone noncompliance and clinical outcome in adult liver transplant recipients

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ABSTRACT

There are limited data concerning the influence of medication noncompliance on clinical outcome in liver transplantation recipients. The aim of this study was to investigate the influence of prednisolone noncompliance, as measured by electronic monitoring (EM), on clinical outcome and hospitalizations during a follow-up period of two years in 108 adult liver transplant recipients.

Except for a somewhat higher alkaline phosphatase in patients who showed the lowest level of compliance in view of Taking and Dosing compliance as well as Drug Holidays, we found no relationship between compliance parameters and liver tests, acute rejection episodes, decrease in immunosuppression, hospital admissions, and patient and graft survival during the two years of follow-up.

In conclusion, in contrast to renal and heart transplantation where minimal deviations in dosing schedule were associated with poor clinical outcome our findings show that the level of noncompliance in this sample of liver transplant recipients was no risk factor for poor clinical outcome. A clinical relevant level of noncompliance in liver transplantation needs to be evaluated in further research.

INTRODUCTION

Compliance can be defined as "the extent to which a person's behaviour - taking medications, following a diet and/or executing lifestyle changes - corresponds with agreed recommendations from a health care provider" [1].

Noncompliance is increasingly recognized as a major long-term problem in solid organ transplantation as the failure rates from other causes have diminished [2]. However there is limited evidence of the influence of medication noncompliance on clinical outcome in adult liver transplant recipients. Only few small retrospective studies [3-5] assessed the influence of medication noncompliance in view of clinical outcome in the liver transplant population. The presence of medication noncompliance in these retrospective studies was based on patient interviews, collateral reports, or the presence of subtherapeutic levels of cyclosporine. Previous research in the solid organ transplantation population with EM showed that minimal deviations from dosing schedule were associated with increased risk for poor clinical outcome in renal [7] and heart [8,9] transplant populations. Noncompliance has also been found to be associated with poor economic outcome [10].

In a previous study [6] we measured prednisolone noncompliance prospectively by EM, the most sensitive and reliable measurement method to date, among 108 adult liver transplant recipients. The results are summarized in Table 1. If optimal compliance is considered to be at the level of 100%, an important issue is at what level noncompliance becomes clinically relevant. Medication noncompliance must have a measurable effect on the outcome for the patient or the graft for it to be clinically relevant [2]. The aim of this prospective cohort study is therefore to investigate the influence of prednisolone noncompliance in liver transplant patients, as measured by EM, on clinical outcome and hospitalizations during a follow-up period of two years.

Table 1. Prevalence of prednisolone compliance, measured by electronic event monitoring in 108 patients during a 4 months period. Percentiles and ranges.

	Lowest*	P10	P25	P50	P75	P90	Highest**
Taking compliance (%)#	59.6	94.4	98.3	100.0	100.0	100.8	105.0
Dosing compliance (%)	57.6	91.6	97.2	99.2	100	100	100
Timing compliance (%)	42.4	66.9	86.7	94.4	98.4	100	100
Drug holiday ≥48 hrs (number per 3 months)	14	4	1	0	0	0	0
Drug holiday ≥72 hrs (number per 3 months)	10	1	0	0	0	0	0

** or highest number in case of Drug holidays; ** or lowest number in case of Drug holidays*
 # for definitions see Patient and Methods section

PATIENTS AND METHODS

Patient characteristics

As described before [6], the study group consisted of 108 patients, who used 10 mg of prednisolone once daily as part of the immunosuppressive regimen, and were in a stable clinical situation in an out-of-hospital setting at the time of compliance measurement. Median age was 47 years (range 22-71); 61% of the patients were female. The median follow-up after liver transplantation was 4 years (range 1-18). Primary liver diseases were primary biliary cirrhosis (19% of patients), primary sclerosing cholangitis (22%), auto-immune cirrhosis (15%), cryptogenic cirrhosis (11%), alcoholic cirrhosis (6%), and other diagnoses (27%). Immunosuppressive regimens consisted of prednisolone/azathioprine/cyclosporine (56% of patients), prednisolone/azathioprine (36%), prednisolone/cyclosporine (7%), and prednisolone/tacrolimus (1%). Patient characteristics with respect to compliance with the daily intake of 10 mg prednisolone, as measured by EM during a four months period, and as described before [6], are listed in Table 1. In short, EM consists of a medication bottle fitted with a cap containing a microelectronic circuit registering the date and time of every bottle opening. Openings of the bottle are recorded as presumptive doses. Stored data can be downloaded to a personal computer for further analysis. Compliance measurements included Taking compliance (TC) which describes the percentage of bottle openings compared with the total number of doses (openings) prescribed. Dosing compliance (DC) describes the percentage of days on which the patient has correctly opened the bottle as prescribed. Timing compliance (TIC) describes the percentage of days that opening of the bottle was within three hours of the subject's chosen time of day to routinely take their prednisolone. A drug holiday (DH) was defined as no medication intake during two (DH48) or three (DH72) consecutive days.

Outcome parameters

The following clinical outcome parameters were studied in relation to medication compliance.

- Liver tests (Alkaline Phosphatase (APh), alanine aminotransferase (ALAT), gammaglutamyltransferase (GGT), total bilirubin (TB)) as determined at baseline, and one and two years later.
- Presence and number of biopsy proven episodes with acute rejection, for which treatment was needed, during two years of follow-up.
- Change in dosages of immunosuppression after two years, as a decrease in dosages might reflect the patient with stable liver tests and good compliance.
- Reasons, frequency and total number of days of hospital re-admissions during the two years of follow-up.
- Patient and graft survival during two years of follow-up.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences 11.5 (SPSS Inc., Chicago, Il, USA). Descriptives, Spearman rank correlation, Mann

Whitney U Test, Friedman Test and Wilcoxon Signed Ranks Test were used where appropriate. A p-value below or equal to 0.05 was considered to indicate statistical significance. A p-value between 0.05 and 0.10 was considered a statistical trend.

RESULTS

Outcome parameters

Liver tests. Median and ranges of the liver tests APh, ALAT, GGT, and TB are listed in Table 2. Median values were within the limits of normality, but the percentages of patients with abnormal liver tests, before and after one and two years of follow-up, was for APh 23, 21, and 18 %, for ALAT 31, 29, and 31 %, for GGT 42, 40, and 39 %, and for TB 14, 16, and 20 %, respectively. No statistical differences were found between the years, except for TB which was higher at two years compared to baseline and at one year.

Acute rejection episodes. Only one of the patients experienced a biopsy proven episode of acute rejection (grade 1) twelve months after inclusion in the study which responded well to an increase of immunosuppression.

Table 2. Liver tests at baseline, and 1 and 2 years later.
Respectively n = 108, 107, and 106 patients. Median and ranges.

		Median	Range	p-value +
APh (13-120 U/l)	baseline	76	30-506	NS
	1 year follow-up	78	33-411	
	2 year follow-up	72	33-426	
ALAT (0-30 U/l)	baseline	22	6-258	NS
	1 year follow-up	22	7-355	
	2 year follow-up	24	6-206	
GGT (0-65 U/l)	baseline	50	7-654	NS
	1 year follow-up	46	7-935	
	2 year follow-up	48	7-769	
TB (3-26 µmol/l)	baseline	16	7-81	0.001
	1 year follow-up	16	6-85	
	2 year follow-up	17	8-96*	

APh: alkaline phosphatase
ALAT: alanine aminotransferase
GGT: gamma glutamyltransferase
TB: total bilirubine
Plus normal values

+ Friedman Test
** Wilcoxon Signed Ranks Test:significantly higher compared to 1 year and baseline (p 0.019 and 0.000 respectively)*

Table 3. Liver-related reasons for re-admission

Bile duct problems	11
Elevated liver function tests	6
Decompensated liver disease	2
Complication after liver biopsy	1
Liver abscess	1

Decrease of immunosuppression. After two years of follow-up, compared to baseline, a substantial decrease of immunosuppression was achieved in 21 patients (19.4%). Seventeen patients with an initial triple drug regimen with prednisolone, azathioprine, and cyclosporine succeeded to wean off the cyclosporine. And in four patients prednisolone was decreased. In only one of the patients the amount of immunosuppressives was higher after two years, and this was the patient who experienced an episode of acute rejection.

Hospital admissions. Twenty (18.5%) of the patients were admitted 38 times during the two year study period.The median duration of hospital stay was 12 days (range 2-139). Reasons for admission were related to liver problems in 21/38 (55.3%), abdominal problems in 7/38 (18.4%), infection in 6/38 (15.8%), and miscellaneous in another 4/38 (10.5%) admissions. More specific information on liver-related problems is provided in Table 3.

Patient and graft survival. One patient died of metastatic colon cancer, 15 months after inclusion in the study. One graft was lost due to acute hepatic artery thrombosis, four months after inclusion in the study; this patient was retransplanted and survived.

Relationship between medication compliance and outcome parameters

Liver tests. Using rank correlation, only for APh significant, although weak correlations were found with several compliance parameters. At baseline a negative correlation was found between APh and TC ($p=0.024$, $r= -.216$), and between APh and DC ($p=0.014$, $r= -.236$). In addition, at baseline a positive correlation was found between APh and DH48 ($p=0.033$, $r= .206$). At 1 year only a statistical trend was found between APh and DC. At 2 years APh was negatively correlated with DC ($p=0.049$, $r= -.192$), and only statistical trends were present for TIC, TC, and DH48.
The weak correlation between APh at baseline and TC, DC, and DH48 is illustrated in Figures 1, 2, and 3, with use of an arbitrary division of the patient population into 4 subgroups. It is shown that subgroup analysis shows only significant differences between the best and the worst compliance group.

Acute rejection episodes. As only one patient experienced an acute rejection episode a possible relation with level of compliance could not be studied in this respect. The DC of this patient was 98,0% and TIC was 87,2%. One DH48 and one DH72 was registered.

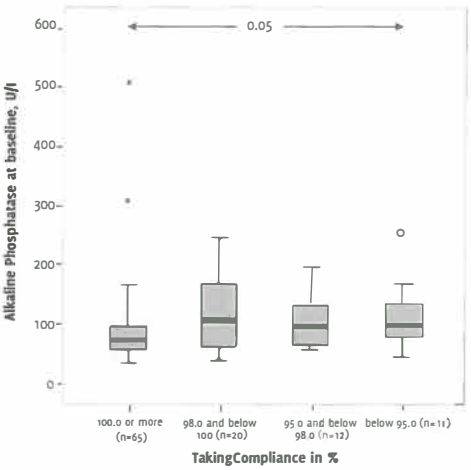

Figure 1. Boxplot of Taking Compliance (n=108) divided into 4 subgroups in relationship with Alkaline Phosphatase at baseline.

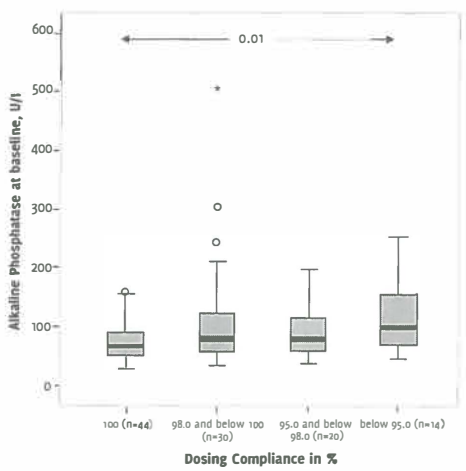

Figure 2. Boxplot of Dosing Compliance (n=108) divided into 4 subgroups in relationship with Alkaline Phosphatase at baseline.

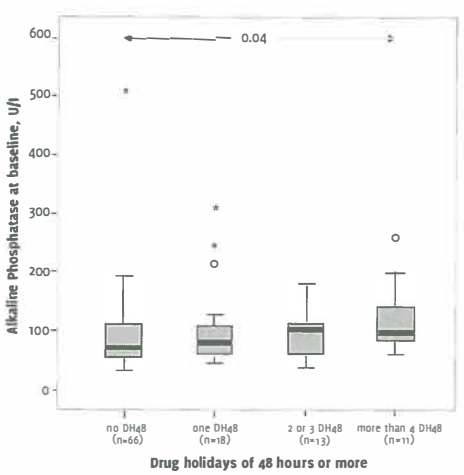

Figure 3. Boxplot of Drug holidays of 48 hours or more (n=108) divided into 4 subgroups in relationship with Alkaline Phosphatase at baseline.

Decrease in immunosuppression. Compliance outcomes did not differ between patients who managed a decrease in immunosuppression during the 2 years of follow-up versus those who did not.

Hospital admissions. Compliance outcomes did not differ between patients who had hospital re-admissions versus those who had none.

Patient and graft survival. As only one patient died, and one additional patient was retransplanted a relationship with level of compliance could not be studied in this respect.

DISCUSSION

The main finding of this prospective cohort study in liver transplant recipients is that no adverse relationship between prednisolone noncompliance, as measured by EM, and clinical outcome could be established.

Only few studies have reported the impact of medication noncompliance after liver transplantation and all were retrospective studies in which noncompliance was measured in various ways. Schweizer *et al.*[3] was one of the first authors to report a possible connection between medication noncompliance and outcome after liver transplantation. Three patients out of a small sample of 13 liver transplant recipients were repeatedly noncompliant with medications; two of these patients died. Mor *et al.*[4] reported an increase of late acute rejection in patients with subtherapeutic cyclosporin levels; in about 40% of cases this was related to medication noncompliance. Rabkin *et al.*[5] studied 40 cases of late death after liver transplantation; one death was related to discontinuation of medication. A retrospective chart review among pediatric liver transplant recipients revealed that four of 23 late deaths were related to noncompliance [11]. Falkenstein *et al.*[12], reviewing pediatric patients records, found that liver tests abnormalities related to noncompliance in 17% of cases. However, no specific details about the values of the liver tests were highlighted. In a retrospective chart review of 32 adolescents who were 10 years or more after liver transplantation suboptimal compliance to immunosuppressive treatment and attendance at follow-up visits was noted in seven adolescents; late acute rejection episodes were found in two of the seven, and chronic rejection in three of them [13].

In contrast to these studies we looked prospectively for a relationship between compliance parameters and clinical outcome. The methodology of the present study also differed as we used EM for compliance measurement. Compliance with the use of prednisolone was overall high in our sample [6].

Except for a somewhat higher APh at baseline in patients who were less compliant, we found no relationship between compliance parameters and liver tests, acute rejection episodes, decrease in immunosuppression, hospital admissions, and patient and graft survival during the two years of follow-up. Probably the lack of compliance in our

study participants was of such a mild degree, that it had no clear detectable adverse effects.

The finding that the respondents with the worst Taking and Dosing compliance and the respondents with the most DH48 had a significant higher APh at baseline compared to excellent compliers might illustrate an association, although weak, with clinical relevance. An elevated APh may reflect immunological damage of bile ducts associated with rejection. However, as a relationship between compliance and the other liver tests was not found, and as in most patients the APh remained within normal limits a relationship with (sub)clinical rejection seems unlikely.

It is remarkable that the strongest correlation between APh levels and compliance parameters were found at baseline, i.e. at the start of the study period. This might indicate that participation in the study induced an improved compliance and that compliance of those, least compliant during the study period, was even less before the study.

In comparison with prospective compliance studies with a 5-year follow-up in adult renal [7,14] and adult heart [9] transplant recipients in which minor deviations of dosing schedule were associated with poor clinical outcome, the findings of this study highlight a different impact of noncompliance on clinical outcome in liver transplant recipients. Nevins *et al.*[7] found that reduced azathioprine compliance was highly associated with acute rejection and allograft loss in a study among renal transplant recipients. Another study[14] among renal transplant recipients describes the association between noncompliance, late acute rejection and a higher increase in serumcreatinine. In the study among heart transplant recipients Dobbels *et al.*[9] reported that noncompliance is a continuous risk factor which doubles the risk for an untoward clinical event.

As it turns out that our patient group was sufficiently compliant for clinical purposes, we could not deduce at what level of compliance as measured by EM, lack of it becomes clinically relevant. The same is true with respect to hospital re-admissions and health care costs.

It is concluded from the present study that the level of noncompliance in our patient group was not of real clinical relevance. DC and TC rates between 95 and 100% did not lead to liver dysfunction or other adverse effects. Lowest compliance rates in our patient group were present for TIC, but TIC rates as low as 70% do not seem to be harmful. The same is true for DHs; one or two DHs (of two days) per three months seem without consequences. Nevertheless, patients should be advised and encouraged to be maximally compliant to their prescribed medication, and compliance should be regularly checked, in order to ensure that no adverse effects due to lack of compliance will arise.

REFERENCES

1. World Health Organization. *Adherence to long-term therapies. Evidence for action.* Section 1. Switzerland, 2003;17-19.
2. Chapman JR. Compliance: the patient, the doctor, and the medication? Transplantation 2004;77:782-86.
3. Schweizer RT, Rovelli M, Palmeri D, Vossler E, Hull D, Bartus S. Noncompliance in organ transplant recipients. Transplantation 1990; 49:374-77.
4. Mor E, Gonwa Th A, Husberg B S, Goldstein RM, Klintmalm GB. Late-onset acute rejection in orthotopic liver transplantation - associated risk factors and outcome. Transplantation 1992;54:821-24.
5. Rabkin JM, La Melena de V, Orloff SL, Corless CL, Rosen HR, Olyaei A. Late mortality after orthotopic liver transplantation. Am J Surg 2001; 181:475-79.
6. Drent G, Haagsma EB, De Geest S, Berg van den AP, Ten Vergert EM, Bosch van den HJ, Slooff MJH, Kleibeuker JH. Prevalence of prednisolone (non) compliance in adult liver transplant recipients. Transpl Int 2005;18:960-66.
7. Nevins Th E, Kruse L, Skeans MA, Thomas W. The natural history of azathioprine compliance after renal transplantation. Kidney Int 2001;60: 1565-70.
8. De Geest S, Abraham I, Moons Ph, Vandeputte M, Van Cleemput J, Evers G ,et al. Late acute rejection and subclinical noncompliance with cyclosporine therapy in heart transplant recipients. J Heart Lung Transplant 1998;17:854-63.
9. Dobbels F, De Geest S, Van Cleemput J, Droogne W, Vanhaecke J. Effect of late medication non-compliance on outcome after heart transplantation: A 5-year follow-up. J Heart Lung Transplant 2004;23:1245-51.
10. Cleemput I, Kesteloot K, Vanrenterghem Y, De Geest S. The economic implications of non-adherence after renal transplantation. PharmacoEconomics 2004;22:1217-34.
11. Sudan DL, Shaw BW Jr., Lagnas AN. Causes of late mortality in pediatric liver transplant recipients. Ann Surg 1998;227:289-95.
12. Falkenstein K, Flynn L, Kirkpatrick B, Casa-Melley A, Dunn S. Non-compliance in children post-liver transplant. Who are the culprits? Pediatr Transplant 2004;8:233-36.
13. Avitzur Y, De Luca E, Cantos M, Jiminez-Rivera C, Jones N, Fecteau A, Grant D, Lee Ng V. Health status ten years after pediatric liver transplantation-Looking beyond the graft. Transplantation 2004;78:566-73.
14. Vlaminck H, Maes B, Evers G, Verbeke G, Lerut E, Van Damme B, et al. Prospective study on late consequences of subclinical non-compliance with immunosuppressive therapy in renal transplant patients. Am J Transplant 2004;4:1509-13.

LETTER TO THE EDITOR

Prednisolone noncompliance and outcome in liver transplant recipients

Recently, we reported on the prevalence of prednisolone noncompliance in liver transplant recipients as measured by electronic monitoring[1]. In the group of 108 adult patients, a median of 4 years after transplantation, the median taking compliance was 100% (range 60-105), median dosing compliance was 99% (range 58-100), and median timing compliance was 94% (range 42-100). A drug holiday of ≥ 48 h was found in 39% of the patients, of ≥ 72 h in 16% of the patients. After 2 years of follow-up we now report on the possible influence of the measured noncompliance on clinical outcome. The following parameters of outcome were studied: liver tests as determined at baseline, and 1 and 2 years later; biopsy proven episodes of acute rejection for which treatment was needed; change in dosages of immunosuppression; hospital re-admissions, and patient and graft survival. Only one patient experienced an episode of rejection; 19% of patients achieved a substantial decrease of immunosuppression after 2 years; 19% of patients were hospitalized for several reasons; one patient died and another one received a second transplant. Except for a somewhat higher alkaline phosphatase (APh) in patients who showed the lowest level of compliance, we found no relations between the compliance parameters and outcome. Using rank correlation, at baseline a weak negative correlation was found between APh and taking compliance ($p=0.024$, $r=-0.216$), and between APh and dosing compliance ($p=0.014$, $r=-0.236$). A positive correlation was found at baseline between APh and drug holidays of ≥ 48 h ($p=0.033$, $r=0.20-6$). At 2 years of follow-up APh was negatively correlated with dosing compliance ($p=0.049$, $r=-0.192$). See Figure 1 for illustration.

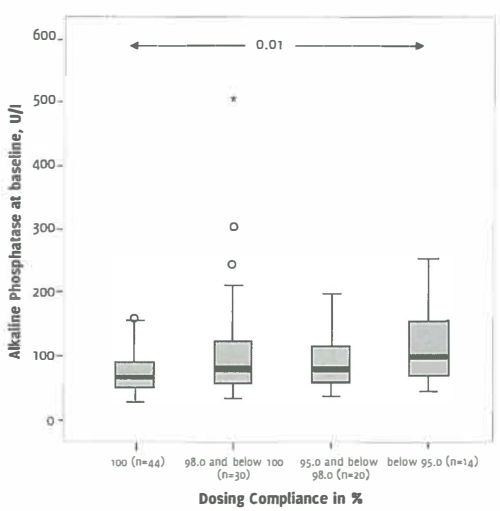

Figure 1. Boxplot of Dosing Compliance (n=108) divided into four subgroups in relation to Alkaline Phosphatase at baseline.

From the present study it may be concluded that the level of prednisolone noncompliance of our liver transplant patients was not of significant clinical relevance. This is in contrast to findings in adult renal [2,3] and adult heart [4,5] transplant recipients, in which minor deviations of dosing schedule were associated with poor clinical outcome. An explanation might be found in that the liver is considered to be a privileged organ in immunological terms. The level of noncompliance with immunosuppressive drugs at which clinical outcome declines after liver transplantation remains to be elucidated in further studies.

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REFERENCES

1. Drent G, Haagsma EB, De Geest S, Van den Berg AP, Ten Vergert EM, Van den Bosch HJ, Slooff MJH, Kleibeuker JH. Prevalence of prednisolone (non-)compliance in adult liver transplant recipients. *Transplant Int* 2005; 18: 960.
2. Nevins TE, Kruse L, Skeans MA, Thomas W. The natural history of azathioprine compliance after renal transplantation. *Kidney Int* 2001; 60: 1565.
3. Vlaminck H, Maes B, Evers G, *et al*. Prospective study on late consequences of subclinical non-compliance with immunosuppressive therapy in renal transplant patients. *Am J Transplant* 2004; 4:1509.
4. De Geest S, Abraham I, Moons PH, *et al*. Late acute rejection and subclinical noncompliance with cyclosporine therapy in heart transplant recipients. *J Heart Lung Transplant* 1998; 17: 854.
5. Dobbels F, De Geest S, Van Cleemput J, Drooge W, Vanhaecke J. Effect of late medication non-compliance on outcome after heart transplantation: a 5-year follow-up. *J Heart Lung Transplant* 2004; 23: 1245.

CHAPTER 5

Symptom experience associated with immunosuppressive drugs after liver transplantation in adults: possible relationship with medication noncompliance?

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ABSTRACT

Symptom experience (occurrence and perceived distress) associated with side effects of immunosuppressive medications in organ transplant patients may well be associated with poorer quality of life and medication noncompliance. The aims of this study were: first, to assess symptom experience in clinically stable adult patients during long-term follow-up after liver transplantation; and second, to study the relationship between symptom experience and medication noncompliance. This cross-sectional study included 123 liver transplant patients. Symptom experience was assessed using the 'Modified Transplant Symptom Occurrence and Symptom Distress Scale' (29-item version) at the annual evaluation. According to the duration of follow-up, patients were divided into a short-term (1-4 yr) and a long-term (5-18 yr) cohort. Medication noncompliance was measured using electronic monitoring. Results showed that increased hair growth was the most frequent symptom in both sexes. Symptom distress was more serious in women than in men. The most distressing symptom in women was excessive and /or painful periods, while in men this was impotence. Clear differences were revealed at item level between symptom occurrence and symptom distress in relationship with the two time cohorts and between sexes. No relationship was found between symptom experience and prednisolone noncompliance.

INTRODUCTION

Orthotopic liver transplantation has gradually become a standard procedure with an increasing number of long-term survivors [1]. Liver transplantation aims to improve survival and perceived quality of life, but it is evident that the transplantation is a life-changing procedure due to the complexity and life-long duration of treatment [1,2].
Liver transplantation necessitates lifelong intake of immunosuppressive medications, which have a broad range of side effects [3-6]. Side effects are generally registered and treated by physicians from the perspective of clinical outcomes, particularly in terms of morbidity and mortality [7]. From the viewpoint of patients, side effects, such as gingival hyperplasia, sexual dysfunctioning and muscle weakness, can be very disturbing and can interfere with health-related quality of life and medication compliance [7-15]. The assessment of patients' perceived symptom experience associated with side effects of immunosuppressive medications is therefore very important as part of overall quality of life assessment [7,11,15]. For example, Rosenberger *et al.* found that fewer side effects of immunosuppression predicted a better mental component of perceived health status in patients younger than 40 yr [15]. Symptom experience can be considered as a patient-reported outcome. Patient-reported outcomes are widely recognized as unique indicators of the impact of disease and of the efficacy of the treatment [16]. Moons *et al.* adapted the Transplant Symptom Occurrence and Symptom Distress Scale, which was developed by Lough *et al.* [8,9] to measure symptoms associated with side effects of immunosuppressive medication (cyclosporine, corticosteroids and azathioprine) through assessing the perceived frequency and distress of the symptoms [17]. This scale has been used in the past to assess symptom experience (symptom occurrence and symptom distress) in heart [10,18], and renal transplant recipients [12,13, 19-22], but so far has not been used in liver transplant recipients. Medication noncompliance is a major issue after organ transplantation and has been found to be associated with an increased risk for acute rejection and graft loss [18,19,23-36].
In an earlier study, we measured the prevalence of prednisolone noncompliance in liver transplant recipients using electronic monitoring [37,38]. However, the association between symptom experience of liver transplant recipients and noncompliance has not been assessed so far.
The aims of this study were therefore: first, to assess symptom experience associated with side effects of immunosuppressive drugs in clinically stable adult patients during long-term follow-up after liver transplantation, with special emphasis on gender differences and in relation to duration of follow-up after transplantation; and second, to study a possible relationship between symptom experience and medication non-compliance.

PATIENTS AND METHODS

Over the course of 1 yr, adult patients who had been followed-up for at least one yr after liver transplantation were asked to participate in the main study on prevalence, determinants and consequences of noncompliance after liver transplantation. The study was approved by the Medical Ethics Committee of the University Medical Center Groningen, The Netherlands. For the study of noncompliance with immunosuppressive drugs, noncompliance with the daily intake of 10 mg prednisolone, was assessed using electronic event monitoring during a four month period, and the results have been described previously[37,38]. Inclusion criteria for the main study were age 18 yr or older, stable clinical situation in an out-of-hospital setting, use of 10 mg prednisolone once daily as part of the immunosuppressive regimen, literacy (Dutch language), and written informed consent. One hundred and forty-two patients were eligible to participate in the study. The patients were invited to participate during their protocolled annual check after liver transplantation and were subsequently enrolled. From the medical records, data were collected concerning date of transplantation, gender, age, primary liver disease, type and dosage of immunosuppressive drugs, and non-immunosuppressive drugs at the time of the annual check. The duration of follow-up was arbitrarily divided in a short-term cohort (1-4 yr) and a long-term cohort (5-18 yr) based on the median duration of follow-up (4 yr). The questionnaire concerning symptoms related to immunosuppressive drugs was given to participants to complete at home. The completed questionnaire could be returned by mail, free of charge.

Symptom experience

Symptom experience (symptom occurrence and symptom distress) associated with side effects of immunosuppressive medication was measured using the translated and adapted version of the Transplant Symptom Occurrence and Symptom Distress Scale[8,9] by Moons et al.[17]. The Modified Transplant Symptom Occurrence and Symptom Distress Scale (MTSOSDS) includes 29 symptoms associated with side effects of immunosuppressive medication (cyclosporine, corticosteroids and azathioprine) and measures the perceived occurrence and distress levels of the 29 tested symptoms[17]. This scale differs for men and women on one item: impotence for men and/or excessive or painful periods for women. Items were scored on a 5-point Likert scale from 0 to 4: from never to always for symptom occurrence; and from not-at-all-distressing to very-much-distressing for symptom distress. To enhance the independence of responses to items about occurrence and distress items, a vertical scaling method was used to rate symptom occurrence, while a horizontal method was used for symptom distress[17] (see Table 1). Validity of the 29-item MTSOSDS has been established by determining whether the scale discriminates symptom experience between renal transplant recipients and healthy controls[17]. Items were reviewed for their clinical relevance by experts in the field.

Table 1. The Modified Transplant Symptom Occurrence and Distress Scale: example of item scoring (item 19)[11].

I have a poor concentration	The inconvenience caused by my poor concentration is
☐ never	not distressing at all — terribly distressing
☐ occasionally	
☐ regularly	
☐ almost always	0____1____2____3____4
☐ always	

1 Acne
2 Poor vision
3 Fever
4 Depression
5 Increased appetite
6 Diarrhea
7 Impotence/Painful and/or very heavy periods
8 Gingival hyperplasia
9 Swollen ankles
10 Moon face
11 Decreased interest in sex
12 Back pain
13 Stomach complaints
14 Changed appearance
15 Mood swings
16 Cough
17 Changed facial features
18 Fragile skin
19 Poor concentration
20 Increased hair growth
21 Sleeplessness
22 Muscle weakness
23 Headache
24 Tremor
25 Fatigue
26 Bruises
27 Pain when passing water
28 Skin rash
29 Muscle cramps

Prednisolone noncompliance

We have previously reported on the prevalence of prednisolone noncompliance as measured prospectively in 108 patients by electronic monitoring (Aardex® Ltd., Zug, Switzerland) during a four month period [37]. A median of 4 yr after transplantation, the range of taking compliance was between 60 % and 105 % (median 100%), the

range of dosing compliance was between 58 % and 100% (median 99%), and the range of timing compliance was between 42 % and 100% (median 94%). A drug holiday of more than 48 h was found in 39% of the patients, and of more than 72 h in 16% of the patients.

Statistical analysis

Data were checked for normality. Mean, standard deviation, median, and percentiles (P25; P75) were calculated as appropriate. For a two-group comparison the t-test, Mann-Whitney U-test, chi-squared or Fisher exact test were used as appropriate. A p-value below or equal to 0.05 was considered to indicate statistical significance. Statistical analysis was performed using the Statistical Package for the Social Sciences 11.5 (SPSS Inc., Chicago, IL, USA).

Symptom experience was analyzed by means of ridit analysis, a method to compare distributions of an ordinal response variable in different groups [39]. A ridit represents the Relative probability to an Identified Distribution and offers a useful interpretation of the probability that a randomly selected individual of the group under investigation scores higher on the response variable than does a randomly selected individual of the reference group [39]. According to the instruction of Moons [10] the reference group in this study was achieved by using the occurrence distribution of the whole sample over all items for comparison among symptoms and over the respective symptoms for comparison of men and women at item level. The data were analyzed at item level by calculating a ridit for each symptom of the instrument to rank-order the most frequent and distressing symptoms. The reliability and validity of the MTSOSDS for this study was tested by means of factor analysis and reliability analysis. The t-like-test developed for ridit analysis by Sermeus and Delesie [39] was used for a 2-group comparison on 28 of the 29 items. The item on *Impotence/Painful and/or very heavy periods* was excluded from this comparison. To protect against the Type 1 error we used a Bonferroni correction. We divided the level of significance by the number of comparisons we would make (0.05/28=0.00178). For a comparison to be significant, it must have a significance level of $\leq$ 0.00178 ($\approx$0.002), not $\leq$ 0.05. To study a possible relation between the number of symptoms and medication noncompliance using chi-squared and Mann Whitney U-test, we divided the patients in groups along the 25th percentile for the highest number of symptoms, and along the 25th percentile for the lowest compliance.

RESULTS

Patient group

Informed consent was obtained from 123 patients. Median age was 46 yr (range 22-71 yr); 76 women and 47 men participated in the study. The median follow-up after liver transplantation was four yr (range 1-18 yr). Primary liver diseases were primary biliary cirrhosis (19% of patients), primary sclerosing cholangitis (21%), autoimmune cirrhosis (15%), cryptogenic cirrhosis (11%), alcoholic cirrhosis (6%), and

Table 2. Patient characteristics: comparison between women and men.

	Women (n=76)	Men (n=47)	p-value
Age (years, median and range)	46.5 (22-71)	48.0 (22-66)	NS
Follow-up (years, median and range)	5.0 (1-18)	3.0 (1-15)	0.001
Primary liver disease (%)			
Primary biliary cirrhosis	30.3	0	
Primary sclerosing cholangitis	13.2	34.0	≤0.001
Other	56.6	66.0	
Number of medications (median and range)	6 (3-12)	6 (3-11)	NS
Number of administrations (median and range)	10 (4-24)	10 (4-19)	NS
Immunosuppression (%)			
Pred/aza/cya*	48.7	72.3	0.010#
Pred/aza	42.1	23.4	
Pred/cya; Pred/tacrolimus	9.2	4.3	
Other medications (%)			
Osteoporosis prophylaxis	81.6	78.7	NS
Antihypertensiva	21.1	31.9	NS
Benzodiazepines	6.6	6.4	NS

**pred=prednisolone; aza=azathioprine; cya=cyclosporine*
 # triple versus duo immunosuppressive therapy

other diagnosis (28%). Immunosuppressive regimens consisted of prednisolone/azathioprine/cyclosporine (57% of patients), prednisolone/azathioprine (36%), prednisolone/cyclosporine (7%), and prednisolone/tacrolimus (1%). All patients used 10 mg prednisolone daily. The median dose of cyclosporine was 200 mg daily (range 50 – 400 mg), the median dose of azathioprine was 125 mg daily (range 25 to 150 mg). Osteoporosis prophylaxis was used by 81% of patients (mainly calciumcarbonate and vitamin D), antihypertensive medication by 25% of patients (calcium antagonists 13%, β-blockers 9% and a combination of both 3%) and benzodiazepines by 7% of patients.

Comparison of patient characteristics between women and men, and between the different cohorts after liver transplantation is shown in Tables 2 and 3. Follow-up was longer for women than for men. Women used triple immunosuppressive therapy less often than men.

There were more women, more patients with an initial diagnosis of primary biliary cirrhosis, and fewer patients using triple immunosuppressive therapy and antihypertensive drugs in the group with a follow-up of more than four yr (cohort 5-18) than in the other group (cohort 1-4). The number of medications and total administrations were lower in the long-term compared with the short-term cohort.

Table 3. Patient characteristics. Comparison between different time cohorts after transplantation.

	1-4 years	5-18 years	p-value
Number of patients	67	56	NS
Gender (f/m)	32/35	44/12	≤ 0.001
Age (yr, median and range)	46 (22-63)	49 (22-71)	NS
Primary liver disease (n)			
Primary biliary cirrhosis	6	17	0.009
Primary sclerosing cholangitis	15	11	
Other	46	28	
Number of medications (median and range)	7 (4-12)	5 (3-11)	≤ 0.001
Number of administrations (median and range)	12 (6-24)	8 (4-19)	≤ 0.001
Immunosuppression (triple vs duo) (n)			
Pred/aza/cya	60	11	≤ 0.001
Pred/aza	3	40	
Other	4	5	
Other medications (n)			
Osteoporosis prophylaxis	56	43	NS
Antihypertensivaes	24	7	0.003
Benzodiazepines	3	5	NS

Pred, prednisolone; aza, azathioprine; cya, cyclosporine

Symptom experience associated with immunosuppressive drugs

The response rate of the questionnaire was 100%. Overall symptom occurrence and symptom distress could not be calculated because factor analysis showed that the instrument consisted of more than one scale.

Symptom occurrence. All patients reported symptoms associated with side effects of immunosuppressive medication with a mean score of 16 out of 29 (55%) (range 2-27). The prevalence of having symptoms showed no differences between genders. Symptom occurrence after transplantation did not show significant differences between the two time cohorts or between genders.

At item level, Table 4 shows in rank-order of ridits the 10 symptoms most frequently reported by women and men. The prevalence of the listed symptoms is also shown. Increased hair growth, fragile skin, changed appearance, fatigue, back pain, and poor concentration appeared in the top ten for both sexes, increased hair growth being number one in both.

Nine of the 28 symptoms were significantly more often reported by women compared to men. The most prominent symptoms in this respect were: decreased interest in sex, changed facial features, sleeplessness, and bruises. Three symptoms were significantly more often reported by men compared to women: acne, trembling hands and muscle cramps (Fig. 1).

In cohort 1-4 significantly higher ridits ($p \leq 0.001$) were found for acne, poor vision, depression, increased appetite, diarrhoea, moon face, back pain, mood swings, in-

Table 4. The 10 most frequently reported symptoms associated to immunosuppression in rank order of ridits in women and men after liver transplantation.

	Women (n=76)				Men (n=47)			
Rank-order	Symptom	Ridit	Prevalence of symptom occurrence %	Prevalence of symptom distress %	Symptom	Ridit	Prevalence of symptom occurrence %	Prevalence of symptom distress %
1	Increased hair growth	0.687	89	87	Increased hair growth	0.678	78	43
2	Fragile skin	0.676	76	90	Back pain	0.642	77	89
3	Bruises	0.657	84	75	Changed appearance	0.623	66	74
4	Changed appearance	0.648	76	77	Acne	0.610	70	63
5	Fatigue	0.630	85	89	Fragile skin	0.602	65	67
6	Back pain	0.597	77	91	Fatigue	0.597	72	76
7	Decreased interest in sex	0.594	69	74	Muscle cramps	0.579	64	90
8	Moon face	0.589	72	75	Increased appetite	0.575	60	79
9	Sleeplessness	0.566	69	92	Poor concentration	0.571	67	84
10	Poor concentration	0.565	76	88	Poor vision	0.570	65	90

creased hair growth, tremor, fatigue, and muscle cramps, and lower ridits ($p \leq 0.001$) for swollen ankles, cough, fragile skin, sleeplessness, and bruises, in comparison with cohort 5-18.

Male patients in cohort 1-4 scored significantly higher ($p \leq 0.001$) on increased appetite, decreased interest in sex, changed appearance, mood swings, increased hair growth, and fatigue, and lower ($p \leq 0.001$) on fever, and stomach complaints than those in cohort 5-18. Female patients in cohort 1-4 scored significantly higher ($p \leq 0.001$) on fever, depression, increased appetite, moon face, mood swings, and increased hair growth, and lower ($p \leq 0.001$) on swollen ankles, cough, and fragile skin than those in cohort 5-18.

Symptom distress. Of the total number of 1987 reported symptoms corresponding distress was experienced 1669 times (84%) by the respondents. In all other cases symptom occurrence was not associated with symptom distress. The prevalence of distress was significantly higher in women compared with men (88% versus 77%, $p \leq 0.018$). Symptom distress in relation to the two time cohorts after transplantation did not show significant differences. The same was found for men and women separately in this respect.

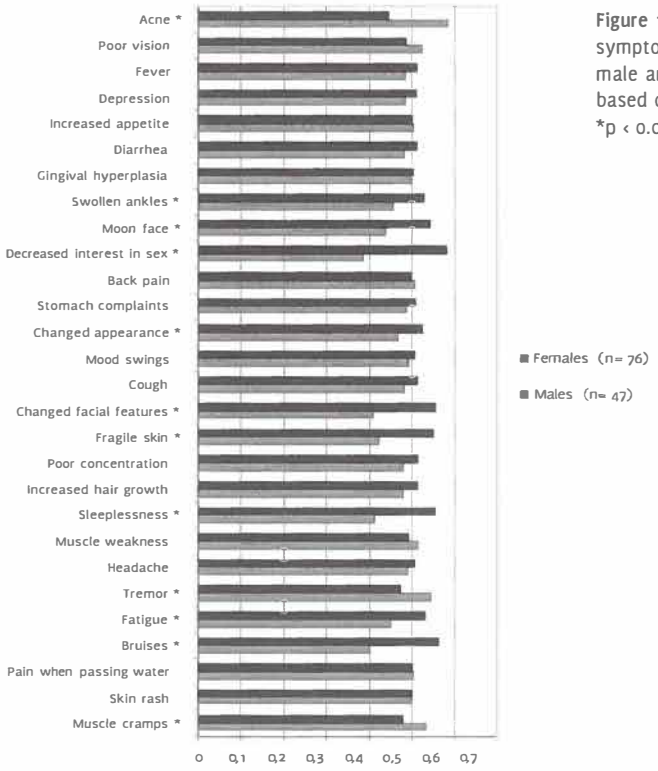

Figure 1. Comparison of symptom occurrence between male and female respondents based on ridit analysis (n=123). *p < 0.002.

At item level Table 5 shows, the 10 most distressing symptoms reported by women and men in rank order of ridits. The prevalence of distress is also shown. The most distressing symptom was excessive and/or painful periods in women and impotence in men. Stomach complaints, muscular weakness, muscle cramps, back pain, and depression showed up in the top ten of both sexes.

Seventeen of the 28 symptoms were significantly more often the cause of distress in women compared with men. Large differences in this respect were found for increased hair growth, changed facial features, cough, moon face and stomach complaints (Fig. 2). In women, the symptoms back pain, poor concentration, sleeplessness and fragile skin were present in the top 10 of both symptom occurrence and symptom distress. In men, the symptoms back pain, muscle cramps and poor vision were present in both top tens.

In cohort 1-4, a significantly higher ridit was found for sleeplessness ($p \leq 0.001$) and significantly lower ridits ($p \leq 0.001$) were found for moon face, cough, changed facial features, increased hair growth, and skin rash, in comparison to cohort 5-18.

Male patients in cohort 1-4 scored significantly higher for mood swings ($p \leq 0.0001$) and lower for increased hair growth ($p \leq 0.0001$) than those in cohort 5-18.

Female patients in cohort 1-4 scored significantly higher ($p \leq 0.001$) on fever and

Table 5. The 10 most distressing symptoms associated to immunosuppression in rank order of ridits in women and men after liver transplantation.

Women (n=76)				
Rank-order	Symptom	Ridit	Prevalence of symptom distress %	Prevalence of symptom occurrence %
1	Painful and/or very heavy periods	0.646	92	37
2	Stomach complaints	0.624	92	34
3	Muscular weakness	0.604	97	49
4	Muscle cramps	0.569	88	56
5	Sleeplessness	0.565	92	69
6	Back pain	0.557	91	77
7	Headache	0.542	91	59
8	Depression	0.535	92	51
9	Poor concentration	0.523	88	76
10	Fragile skin	0.522	90	76

Men (n=47)				
Rank-order	Symptom	Ridit	Prevalence of symptom distress %	Prevalence of symptom occurrence %
1	Impotence	0.677	91	23
2	Back pain	0.633	89	77
3	Stomach complaints	0.633	93	32
4	Pain when passing water	0.624	80	11
5	Fever	0.619	85	28
6	Muscle cramps	0.606	90	64
7	Swollen ankles	0.606	94	34
8	Poor vision	0.605	90	65
9	Depression	0.605	86	47
10	Muscular weakness	0.585	92	56

sleeplessness, and lower ($p \leq 0.001$) on moon face, changed appearance, changed facial features, increased hair growth, and bruises, than those in cohort 5-18.

Possible relationship with medication noncompliance

No relationship was found between the number of symptoms experienced and the level of prednisolone noncompliance. The group including the 25% of patients with the highest numbers of symptoms was not more or less compliant than the group including the other 75% of patients.

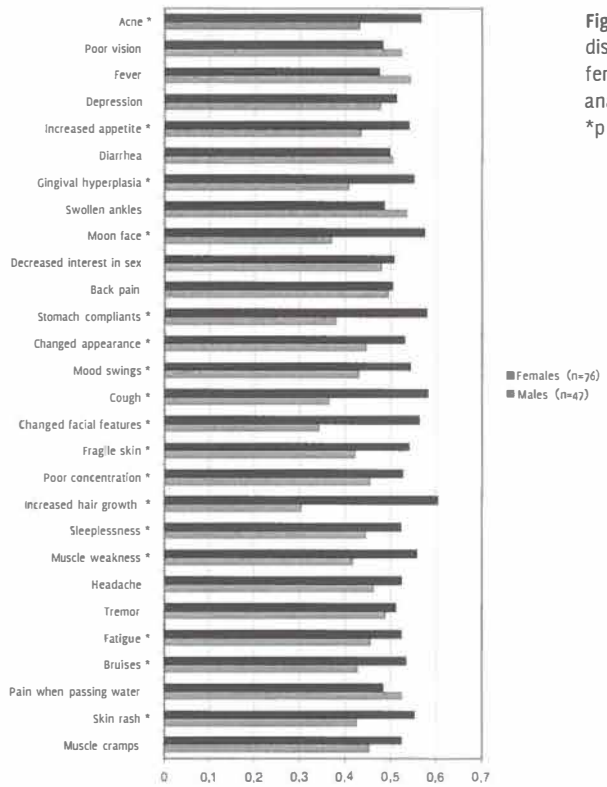

Figure 2. Comparison of symptom distress between male and female respondents based on ridit analysis (n=123)
*p < 0.002

DISCUSSION

Study of symptom experience associated with side effects of immunosuppressive drugs after organ transplantation is of utmost importance in relation to quality of life issues and medication compliance. A study into patients' reasons for discontinuing chronic medication showed that 24.5% out of 93 patients did not refill their prescriptions due to side effects of these medications [14]. There are only limited data about symptom experience and changes over time in liver transplant recipients. This was a cross-sectional study of adult liver transplant recipients with both short-term (1-4 yr) and long-term (5-18 yr) follow-up.

The prevalence of symptoms did not differ between men and women, or between the short-term and long-term time cohorts. At item level increased hair growth was the most frequent symptom in both sexes, most often reported in the short-term cohort. While the prevalence of symptoms was the same for both sexes, symptom distress was more serious in women compared to men, but again there were no differences between the two time cohorts. At item level the most distressing symptom in women was felt to be excessive and /or painful periods, and in men impotence. Stomach, back

and muscle complaints and depression also appeared in the top 10 for both sexes.
The results show clear differences at item level between symptom occurrence and symptom distress, both absolute as over time and between sexes. For example increased hair growth scored high as a symptom in the short-term cohort, but scored high as distress in the long-term cohort. A symptom such as cough becomes apparent both as a symptom and as distress in the long-term cohort. Women in the long-term cohort reported more cosmetic side effects than in the short-term cohort.
The differences between the short- and long-term cohort are likely influenced by the fact that in the long-term cohort relatively more women were present, but also that much less cyclosporine and fewer antihypertensive drugs were used. This may be interpreted as a disadvantage of our cross-sectional study. However, it is very likely that a prospective longitudinal study would also have shown discontinuation of drugs like for example cyclosporine, which is associated with a higher risk for hypertension. In this respect it should be noted that as years pass after transplantation, comorbidity from long-term immunosuppression and from advancing age increases. This is certainly true for cardiovascular disease and malignancies, which by themselves may contribute to a rise of symptoms. This may in part explain why we did not see a decrease in symptom and distress experience in the long-term cohort.
Comparison of our data with those of others is hampered by differences in transplanted organ [10,12,13,19-22], age [20], gender [10,12,13,20,22], duration of follow-up [10,12,13,17,20-22], methodology [20-22] and immunosuppressive regimens [13,21] between studies. Although we did not find an increased symptom occurrence in women compared to men as has been reported previously [10,12,13,19], in this study we did find increased distress among women as in most other studies. In addition, excessive and/or painful periods in women and impotence in men are reported in most studies as the most distressing symptom. When comparing the study data with the results of a heart transplant group[10] it is apparent that fatigue and poor concentration were found in the top ten for the liver transplant recipients, but were absent in the heart transplant ranking list.
Long-term data on the perceived side effects of immunosuppressive medications are available from a renal transplant group [19], but in that study no comparison between short- and long-term follow-up was made.
Experience of symptoms associated with immunosuppressive drugs is expected to have an impact on medication noncompliance. This was shown in a study on renal transplant recipients in which medication noncompliance was assessed by interview[12]. Another study in renal transplant recipients could not confirm a relationship between symptom experience and noncompliance [19]. We measured the prednisolone noncompliance in our patients using electronic monitoring [37] and did not find that patients with most symptoms have the lowest compliance. Overall the compliance was quite high, which either means that symptoms did not influence compliance or that the number of patients with serious noncompliance was too small to find a relationship between symptoms and noncompliance.
The results of this study have several clinical implications. The results provide health care workers with important information regarding the symptom experience with immunosuppressive drugs, and its possible influence on medication compliance.

Furthermore the results can be used to educate the patients about the objective and subjective side effects of these drugs. Last but not least, the perceived symptoms of immunosuppressive medications should be taken into account when developing and prescribing immunosuppressive drugs. However, one has to keep in mind that a causal relationship between symptoms and immunosuppressive drugs cannot always be firmly established and that there may be other factors that influence symptom experience, e.g. other medications such as antihypertensive drugs. The etiological factors of the symptoms experienced were not investigated in this study.

In contrast with previous studies using the MTSOSDS [10,12,13,18-22], we did not calculate overall scores for symptom occurrence and symptom distress. Indeed, factor analysis showed that the instrument consisted of more than one scale. Furthermore, we found negative correlations between some items. Another difference with previous studies is that we, in the present study, have corrected for Type I errors resulting from multiple testing by performing the Bonferroni correction.

In conclusion we found that female liver transplant recipients have a higher degree of perceived symptom distress compared with male liver transplant recipients. A decrease in symptom occurrence and distress in the long term cohort was not apparent. There was no relationship between symptom experience and prednisolone noncompliance.

REFERENCES

1. Karam VH, Gasquet I, Delvast V et al. Quality of life in adult survivors beyond 10 years after liver, kidney and heart transplantation. Transplantation 2003: 76: 1699.
2. Forsberg A, Bädeman L, Möller A. Experiencing liver transplantation: a phenomenological approach. J Adv Nurs 2000: 32: 327.
3. Pless M, Zivkovic SA. Neurologic complications of transplantation. The Neurologist 2002: 8: 107.
4. Rabkin JM, Corless CL, Rosen HR, Olyaei AJ. Immunosuppression impact on long-term cardiovascular complications after liver transplantation. Am J Surg 2002: 182: 595.
5. Lerut JP. Avoiding steroids in solid organ transplantation. Transpl Int 2003: 16: 213.
6. Encke J, Uhl W, Stremmel W, Saner P. Immunosuppression and modulation in liver transplantation. Nephrol Dial Transpl 2004: 19 (Suppl 4):22.
7. De Geest S, Moons P. The patient's appraisal of side-effects: the blind spot in quality-of-life assessments in transplant recipients. Nephrol Dial Transplant 2000: 15: 457.
8. Lough M, Lindsey A, Shinn J, Stotts N. Life satisfaction following heart transplantation. J Heart Transpl 1985: 4: 446.
9. Lough ME, Lindsey AM, Shinn JA, Stotts NA. Impact of symptom frequency and symptom distress on self-reported quality of life in heart transplant recipients. Heart & Lung 1987: 16: 193.
10. Moons P, De Geest S, Abraham I, Van Cleemput J, Vanhaecke J. Symptom experience associated with maintenance immunosuppression after heart transplantation: Patients' appraisal of side effects. Heart & Lung 1998: 27: 315.
11. Moons P, Fairchild S, De Geest S. Patients' appraisal of side effects in quality of life assessments of immunosuppressive regimens. In: Cochat P, et al. Eds. Immunosuppression under Trial. London: Kluwer Academic Publishers, 1999, 69.
12. Texeira De Barros C, Cabrita J. Self-report of symptom frequency and symptom distress in kidney transplant recipients. Pharmacoepidemiology Drug Saf 1999: 8: 395.
13. Moons P, Vanrenterghem Y, Hooff van JP et al. Health-related quality of life and symptom experience in tacrolimus-based regimens after renal transplantation: a multicentre study. Transpl Int 2003: 16: 653.
14. Hugtenburg JG, Blom AThG, Kisoensingh SU. Initial phase of chronic medication use; patients' reasons for discontinuation. Br J Clin Pharmacol 2005: 61: 352.
15. Rosenberger J, Geckova AM, van Dijk JP et al. Prevalence and characteristics of noncompliant behaviour and its risk factors in kidney transplant recipients. Transpl Int 2005: 18: 1072.
16. Acquadro C, Berzon R, Dubois D et al. Incorporating the patient's perspective into drug development and communication: an ad hoc task force report of the patient-reported outcomes (PRO) harmonization group meeting at the Food and Drug Administration, February 16, 2001. Value Health 2003: 6: 522.
17. Moons P, De Geest S, Versteven K et al. Psychometric properties of the Modified Transplant Symptom Occurrence and Symptom Distress Scale. J Nurs Meas 2001: 9: 115.
18. De Geest S, Abraham I, Moons P et al. Late acute rejection and subclinical noncompliance with cyclosporine therapy in heart transplant recipients. J Heart Lung Transpl 1998: 17: 854.
19. De Geest S, Borgermans L, Gemoets H et al. Incidence, determinants, and consequences of subclinical noncompliance with immunosuppressive therapy in renal transplant recipients. Transplantation 1995: 59: 340.
20. Sundberg AK, Smith LD, Somerville KT, Cox R, Sherbotie JR. Conversion from cyclosporine to tacrolimus is preferred by pediatric renal transplant recipients: A focus on opinions and outcomes. Transpl Proc 2002: 34: 1951.
21. Artz MA, Boots JMM, Ligtenberg G et al. Conversion from cyclosporine to tacrolimus improves quality-of-life indices, renal graft function and cardiovascular risk profile. Am J Transpl 2004: 4: 937.
22. Cleemput I, Kesteloot K, Moons P et al. The construct and concurrent validity of the EQ-5D in renal transplant population. Value Health 2004: 7: 499.
23. Didlake RH, Dreyfus K, Kerman RH, Van Buren CT, Kahan BD. Patient noncompliance: a major cause of late graft failure in cyclosporine-treated renal transplants. Transpl Proc 1988: 10 (Suppl 3): 63.
24. Rovelli M, Palmeri D, Vossler E, Hull D, Schweizer R. Noncompliance in renal transplant

recipients:evaluation by socio-economic groups. Transpl Proc 1989: 21: 3979.
25. Rovelli M, Palmeri D, Vossler E, Bartus S, Hull D, Schweizer R. Noncompliance in organ transplant recipients. Transplant Proc 1989: 21: 833.
26. Schweizer RT, Rovelli M, Palmeri D, Vossler E, Hull D, Bartus S. Noncompliance in organ transplant recipients. Transplantation 1990: 49: 374.
27. Swanson AM, Palmeri D, Vossler ED, Bartus SA, Schweizer RT. Noncompliance in organ transplant recipients. Pharmacotherapy 1991: 11: 1735.
28. Mor E, Gonwa Th A, Husberg BS, Goldstein RM, Klintmalm GB. Late-onset acute rejection in orthotopic liver transplantation – associated risk factors and outcome. Transplantation 1992: 54: 821.
29. Sketris I, Grobler M, West M, Gerus S. Factors affecting adherence with cyclosporine in adult renal transplant recipients. Transplant Proc 1994: 26: 2538.
30. Sudan DL, Shaw B W Jr., Lagnas AN. Causes of late mortality in pediatric liver transplant recipients. Ann Surg 1998: 227: 289.
31. Rabkin JM, La Melena de V, Orloff SL, Corless CL, Rosen HR, Olyaei A. Late mortality after orthotopic liver transplantation. Am J Surg 2001: 181: 475.
32. Nevins Th E, Kruse L, Skeans MA, Thomas W. The natural history of azathioprine adherence after renal transplantation. Kidney Int 2001: 60: 1565.
33. AvitzurY, De Luca E, Cantos M et al. Health status ten years after pediatric liver transplantation-Looking beyond the graft. Transplantation 2004: 78: 566.
34. Dobbels F, De Geest S, Van Cleemput J, Droogne W, Vanhaecke J. Effect of late medication noncompliance on outcome after heart transplantation: A 5-year follow-up. J Heart Lung Transplant 2004: 23: 1245.
35. Falkenstein K, Flynn L, Kirkpatrick B, Casa-Melley A, Dunn S. Noncompliance in children post-liver transplant. Who are the culprits? Pediatr Transplant 2004: 8: 233.
36. Vlaminck H, Maes B, Evers G et al. Prospective study on late consequences of subclinical noncompliance with immunosuppressive therapy in renal transplant patients. Am J Transplant 2004: 4: 1509.
37. Drent G, Haagsma EB, De Geest S et al. Prevalence of prednisolone (non) compliance in adult liver transplant recipients. Transpl Int 2005: 18: 960.
38. Drent G, De Geest S, Haagsma, EB. Prednisolone noncompliance and outcome in liver transplant recipients. Letter to the Editor. Transpl Int 2006: 19: 342.
39. Sermeus W, Delesie L. Ridit analysis on ordinal data. West J Nurs Res 1996: 18: 351.

CHAPTER

Current health status of patients who have survived for more than 15 years after liver transplantation

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ABSTRACT

Background: Liver transplantation was started in our centre as early as 1979. We studied the clinical outcome of patients surviving longer than 15 years, with special interest for the broad range of comorbidity and the self-perceived quality of life.

Methods: All patients who underwent a liver transplantation at an adult age, between March 1979 and February 1991, and who had survived at least 15 years were eligible for the study. Data were collected from the medical records. Health-related quality of life was assessed using the Six-Dimensional EuroQol test.

Results: The five-year survival of patients alive 15 years after transplantation was 78%. Thirty-seven patients are currently alive with a median follow-up of 18.8 years (range 15.0-26.8) after transplantation. Comorbidity consists predominantly of overweight (57%), osteoporosis (49%), *de novo* cancer (38%, mainly skin cancer), hypertension (38%), cardiovascular events (19%), diabetes mellitus (22%), cataract (24%), and renal clearance <50 ml/min (11%). Eight patients (22%) underwent a retransplantation, and compensated cirrhosis is present in four patients (11%). The pattern of comorbidity seems to relate to the type of immunosuppression which consisted mainly of prednisolone and azathioprine. Quality of life was perceived as satisfactory (7 on a scale of 0 to10). However, about half of the patients reported limitations in the domains mobility, usual activities and pain/discomfort. In addition a minority reported some anxiety or depression.

Conclusion: The outcome of liver transplantation in this early cohort of patients is fairly good. Improvements may be achieved by adaptations in the immunosuppressive regimen.

INTRODUCTION

Liver transplantation has been the accepted therapeutic option for end-stage liver disease for more than 20 years. Over the years, survival rates have improved. A substantial number of patients now survive for more than one or even two decades. However, quality of life may be influenced by long-term side effects of immunosuppressive treatment and by the functional status of the liver graft as *de novo* liver disease or recurrent liver disease might develop. Most studies have focussed on single complications after liver transplantation, e.g. cardiovascular disease or renal disease, mainly in the first decade after the transplant, and are not concerned with the whole spectrum of comorbidity. Only two studies are known to us that report extensively on the health status in patients longer than ten years after liver transplant. [1,2] Patterns of comorbidity might differ between centres in relation to patient characteristics, duration of survival after liver transplantation, and the types of immunosuppressive drugs that are used.
The present study concerns the health status and quality of life of patients who received a liver transplant in our centre between 1979 and 1991 and were alive in February 2006.

PATIENTS AND METHODS

All patients who underwent a liver transplantation in our centre at an adult age (> 17 years), between 1 March 1979 and 1 February 1991, and who survived at least 15 years were eligible for the present study.

Data collection

From the medical records the following basic data were collected: gender, age at transplant, present age, indication(s) for (re)transplant, date(s) of (re)transplant, date of death, and cause of death.
From all patients alive in February 2006, the following data regarding the health status were collected: eye problems, ENT problems, neurological disease, lung disease, cardiovascular disease, hypertension, body mass index, diabetes, gastrointestinal disease, renal and urological disease, gynaecological disease, malignancies, and osteoporosis. The state of the liver was evaluated by most recent liver pathology, radiology, and laboratory tests. Present medication, including the dosages of the immunosuppressive drugs, was noted. Most recent routine laboratory tests were noted, including haematological tests, liver tests, creatinine, creatinine clearance, and total cholesterol.

Immunosuppression

Basically, two immunosuppressive regimens were used for long-term maintenance therapy since the start of our programme in 1979. Until 1986, immunosuppression consisted of azathioprine, 125 to 150 mg/day, and prednisolone in a starting dose of

200 mg/day, which was gradually tapered to a dose of 30 mg/day at six months, 20 mg/day at one year, and 10 mg/day at two years. In 1986 cyclosporine was added, which resulted in a triple drug regimen with lower prednisolone dosages. After the second year we aimed to taper and discontinue cyclosporine in patients with a triple drug regimen. Since 2000 we aim to reduce the prednisolone dose to 5 mg/day and the azathioprine dose to 50 mg/day in patients with long-term survival.

Quality of life

Health-related quality of life was assessed using the Six-Dimensional EuroQol test (EQ-6D) [3,4]. The EQ-6D is a concise test which consists of six dimensions: mobility, self-care, usual activities, pain/discomfort, anxiety/depression, and cognitive functioning. Each dimension has three possible answers: no problems, some problems, and extreme problems. Three questions were added concerning a paid job (yes or no), paid help at home (yes or no), and a numerical expression of self-perceived health status (0 to 10,0 = worst, 10 = best). The questionnaire was sent to the patients by post with the request to participate and to return the list by pre-paid post.

Charlson Comorbidity Index

The Charlson Comorbidity Index (CCI) gives a weighted score that takes into account both the number and the seriousness of a series of diseases. In addition weight is given to age [5]. We used the modified CCI according to Birim *et al.* [6] in which coronary heart disease is not limited to myocardial infarction alone. In short, one point is given for the conditions ccoronary artery disease, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective pulmonary disease, peptic ulcer disease, mild liver disease, and diabetes. Two points are given for hemiplegia, moderate or severe renal disease, diabetes with end-organ damage, any tumour in the last five years, leukaemia, and lymphoma. Three points are given for moderate or severe liver disease. Six points are given for metastatic solid tumour and AIDS. In addition, for each decade > 40 years of age, one point is added.

In the absence of clear definitions, we defined moderate or severe renal disease as a creatinine clearance <50 ml/min, and moderate or severe liver disease as the presence of advanced fibrosis, cirrhosis, and/or portal hypertension.

Statistical analysis

The χ^2 or Fisher's exact test was used to analyze the categorical data. Survival was analyzed by the Kaplan-Meier method. All data were analysed using the Statistical Package for Social Sciences 11.0 (SPSS Inc., Chicago, Illinois, USA). A two-tailed p-value < 0.05 was considered to indicate statistical significance. When not otherwise stated, the results are given in median and range.

RESULTS

Survival after the 15th year

Forty-nine (45.4%) of the 108 adult patients receiving a liver transplantation before 1 February 1991 survived at least 15 years after the transplant. The median age at 15 years was 55.7 years (range 32.4-73.7). After the 15th year seven patients have died so far. Causes of death were cardiovascular in four patients, bacterial sepsis in relation to recurrent cholangitis and intra-abdominal abscess, respectively, in two patients, and colonic cancer in one patient.

The one- and five-year patient survival rates after the 15th year were 89 and 78%, respectively. In this respect there was no difference between patients older or younger than 55 years.

HEALTH STATUS OF THE CURRENTLY ALIVE PATIENTS

Patient characteristics

Five patients moved outside the Netherlands and are excluded from the study because of lack of detailed information. The patient characteristics of the 37 remaining patients are listed in *table* 1. Thirty patients are female. Present age is a median of 57.4 years (range 37.7 – 79.3). The median follow-up after liver transplantation is median 18.8 years (range 15.0-26.8). Most patients were transplanted for autoimmune liver diseases. Eight patients (21.6 %) underwent retransplantations for different reasons.

Long-term medical complications after liver transplant

An overview is depicted in *figure* 1.

Eyes. Nine patients (24.3%) developed a cataract, for which five underwent surgery. One patient developed a glaucoma and one had Sjogren's disease.

ENT. Two patients (5.4%) needed ENT surgery for recurrent sinusitis.

Oral cavity. None of the patients developed (pre)malignancy in the oral cavity.

Lungs. No major lung problems have occurred except that eight patients have had more than one episode of bacterial infection. One patient is suffering from COPD.

Breast. None of the patients developed breast cancer. In one patient a benign tumour was removed; and one patient underwent corrective surgery.

Neurological disorders. One patient suffered from a stroke, peroperatively, with minor long-term sequelae. Two patients had transient ischemic attacks (TIA). One patient is being treated for epilepsy, after having developed a reversible coma associated with the use of cyclosporine in the first year after transplantation.

Cardiovascular system. Fourteen patients (37.8%) are receiving treatment for hypertension. Two patients suffered a myocardial infarction, after which one of them underwent coronary bypass surgery. Another two patients are treated for angina pectoris. Two patients are being treated for intermittent claudication. Overall, including the patients

Table 1. Patient characteristics of 37 patients currently alive more than 15 years after liver transplantation (median and ranges).

Number of patients	37
Gender (female/male)	30/7 (81%/19%)
Age at LT (years)	38.5 (17.3 - 58.7)
Diagnosis of liver disease	
Primary biliary cirrhosis	13 (35%)
Primary sclerosing cholangitis	6 (16%)
Autoimmune cirrhosis	5 (14%)
Cryptogenic cirrhosis	4 (11%)
Budd-Chiari	3 (8%)
Miscellaneous	6 (16%)
Calendar year and month of LT	March 1987 (April 1979 - January 1991)
Follow-up after first LT (years)	18.8 (15.0 - 26.8)
Re-LT:	
Number of re-LT'S	9 re-LT's in 8 patients (21.6%)
First re-LT, years after LT	5.6 (0.0 - 12.9)
Reasons for re-LT:	
HAT	2 (22%)
De novo HCV	2 (22%)
Chronic rejection	2 (22%)
Acute rejection	1 (11%)
ITBL	1 (11%)
PNF	1 (11%)

LT=liver transplantation; HAT=hepatic artery thrombosis; HCV=hepatitis C virus; ITBL= ischemic-type biliary lesions; PNF=primary non-function.

with TIA's, 15 patients (40.5%) developed symptomatic cardiovascular disease. In addition one patient suffered from an episode of rheumatic pericarditis. Ten patients (27%) receive lipid-lowering drugs. The most recently measured serum cholesterol level is 5.31 mmol/l (3.30 to 9.60).

Body mass index. Overweight, defined as BMI ≥ 25, is currently present in 21 patients (56.8%). Seven patients (18.9%) are obese, with BMI >30.

Diabetes mellitus. Six patients developed *de novo* diabetes mellitus type 2 after liver transplant. Including 2 patients with diabetes already before the liver transplant, eight patients (21.6%) are presently being treated for diabetes mellitus.

Upper gastrointestinal tract. Two patients had peptic ulcers. Four patients developed recurrent asymptomatic oesophageal varices. Nineteen patients (51.4%) are using proton-pump inhibitors or H2 blockers. One patient is treated for exocrine pancreatic insufficiency.

Liver disease. See below, under liver graft.

Colon. One patient developed a colon cancer and underwent a hemicolectomy. Another eight patients had adenomatous polyps removed during screening colonoscopies. Four patients had documented with inflammatory bowel disease before the transplant. One of them underwent colectomy after liver transplant because of severe dysplasia.

Kidneys and urinary tract. Two patients developed a renal carcinoma (detected by routine

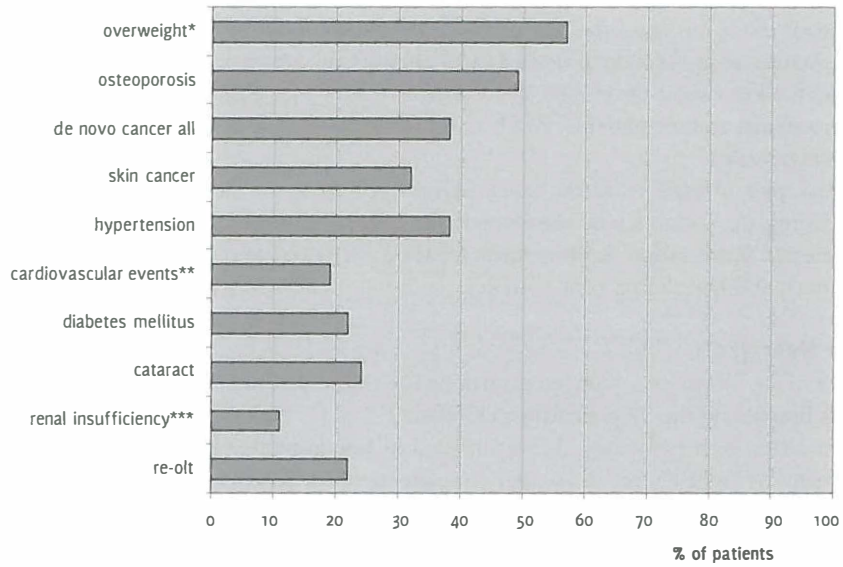

Figure 1. Prevalence of the main comorbidity in 37 patients currently alive more than 15 years after liver transplantation.

* BMI ≥ .25, ** Including myocardial infarction, angina, claudication, and TIAs,
*** creatinine clearance ‹50 ml/min.

ultrasound) for which a nephrectomy was performed. One patient with extensive urogenital condylomata acuminata underwent a cystectomy with an uretero-ileostomy. Eight patients (21.6%) suffered from urinary tract stones. Ten patients were treated more than once for bacterial urinary tract infection. The serum creatinine is 82 µmol/l (42 to133), and the creatinine clearance 80 ml/min (24 to148). Four patients have a clearance <50 ml/min.

Gynaecological disorders. Four of the 30 women had undergone a hysterectomy before liver transplantation. After the transplant, one patient who had surgery is still being monitored closely for extensive condylomata acuminata. Three patients were treated for meno-metrorrhagias. Another three patients were treated for cervical dysplasia. Three patients had successful pregnancies.

Haematological disorders. One patient developed a non-Hodgkin's lymphoma (Epstein-Barr virus negative), which was successfully treated with chemotherapy and anti-CD20. After five years this patient is doing well without signs of recurrence and on low-dose immunosuppression. One patient has anaemia in relation to erythropoietic protoporphyria. Recent laboratory tests show the following blood counts: haemoglobin 8.6 mmol/l (4.0 to 9.9), mean corpuscular volume 94,8 fl (70.9 to 102.1), leucocytes 7.7 10^3/l (range 2.2 to 12.7), platelets 224 10^9/l (61 to 504).

Bone disease. Overall 18 patients (48.6%) are suffering from osteoporosis, defined as T-value <2.5 SD, as measured by bone densitometry. Fifteen of these patients developed the osteoporosis after liver transplant. In 11 patients vertebral osteoporotic fractures occurred. Eight patients suffered from fractures of an arm or leg. Two patients have advanced

arthrosis of the hip and ankle, respectively. One patient received a total hip arthroplasty.
Skin. Actinic keratosis is documented in 17 patients and Morbus Bowen's disease in five patients. Skin cancer developed in 12 patients (32.4%): basocellular in five patients, planocellular in four patients, and both in three patients. One patient uses acetretine (Neotigason®).
De novo cancer. Overall 16 *de novo* cancers developed in 14 of the 37 patients (37.8%). Excluding the patients who developed skin cancer, four of the 37 patients (10.8%) developed *de novo* cancer at other sites: renal cancer (two patients), colon cancer (one patient), and lymphoma (one patient).

The liver graft

Eight of the 37 patients were retransplanted for a variety of reasons (*table* 1). The current graft function in the 37 patients is as follows.
Most recent liver pathology shows cirrhosis in four patients (10.8%), and fibrosis in a greater or lesser degree in another ten patients (27.0%). Four patients (16.2%) have oesophageal varices. None of these patients, however, have decompensated liver disease, defined as the absence of ascites..
Recurrent disease is present in seven patients (18.9%). Recurrent primary biliary cirrhosis (PBC) in an early stage is present in four of the 13 PBC patients (30.7%), recurrent primary sclerosing cholangitis (PSC; non-anastomotic strictures; as judged by MRCP and histology) in two of the 6 PSC patients (33.3%), and one patient had signs of recurrent Budd-Chiari syndrome early after liver transplantation.
Three patients have hepatitis C infection; in all three the virus was acquired in the perioperative period either from the (first) donor liver or from blood products. Two patients have nonanastomotic strictures in the biliary tree.
Eight patients (21.6%) use on ursodeoxycholic acid.
Recent laboratory tests reflecting the function of the liver show the following: alkaline phosphatase 70 U/l (38 to 791), aspartate aminotransferase 30 U/l (15 to 105), alanine aminotransferase 22 Ul (8 to 88), γ-glutamyltransferase 49 U/l (9 to742), bilirubin 13 μmol/l (6 to 44), total protein 69 g/l (58 to 83) and albumin 41g/l (28 to 46).

Medication

At present, the medication includes a median of seven drugs (3 to 20) for a variety of conditions. Per patient a median of five conditions (2 to 12) are being treated with drugs. The immunosuppressive regimen consists of prednisolone/azathioprine in the majority of patients (31 patients, 83.8%). The other patients are taking prednisolone as monotherapy (one patient) or in combination with mycophenolate mofetil (one patient), cyclosporine (one patient), tacrolimus (one patient) or azathioprine/cyclosporine (two patients). The median dose of prednisolone is 10 mg (5-10), and of azathioprine 100 mg (50-125). The combination of prednisolone 5 mg and azathioprine 50 mg, which is presently the lowest dose we aim for after liver transplantation, is being taken by four patients (10.8%).
Other drugs are mainly for cardiovascular disorders and for prevention or treatment of osteoporosis. *See figure* 2 for an overview.

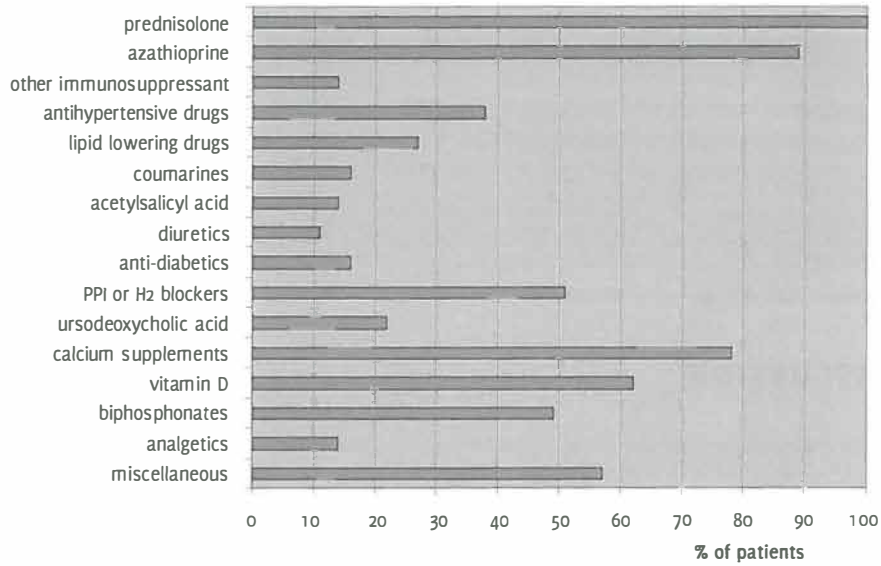

Figure 2. Medication use in 37 patients currently alive more than 15 years after liver transplantation.

Quality of life

The interview on self-perceived quality of life was completed and returned by 35 patients (94.6%). The results of the EQ-6D are listed in *table* 2. It is shown that a large majority of patients have no problems with respect to self care, do not feel anxious or depressed, and have no cognitive symptoms. The majority of patients have no difficulties with their usual daily activities, but a substantial number do have problems. Most patients have some problems with mobility, and suffer from at least some pain and discomfort. Full inability to perform daily activities and serious pain is reported by 11 and 14% of the patients, respectively. Of the patients, 20% have a paid job and 20% makes use of paid help at home.

On the scale of 0 to 10, the self-perceived health status was scored as 7 (4 to 10).

In all these aspects no differences were found between patients older or younger than 55 years, except that more younger patients had a paid job (37.5 *vs* 5.3 %) ($p= 0.032$).

The Charlson Comorbidity Index (CCI) in these 35 patients was 3 (0 to 7). No relation was found between the six domains of the EQ-6D and the CCI. Usual activities and the need for help at home tended to relate to the presence of osteoporosis ($0.05<p<0.10$)

Table 2. Quality of life as measured by the Six-Dimensional EuroQol in 35 patients (number of patients (%).

	No problems	Some problems	Extreme problems
Mobility	15 (42.9)	19 (54.3)	1 (2.9)
Self-care*	29 (82.9)	4 (11.4)	1 (2.9)
Usual activities	19 (54.3)	12 (34.3)	4 (11.4)
Pain/discomfort	13 (37.1)	17 (48.6)	5 (14.3)
Anxiety/depression	27 (77.1)	8 (22.9)	0
Cognition	25 (71.4)	10 (28.6)	0

* Result from one patient is missing

DISCUSSION

Liver transplantations are usually performed in chronically ill patients. As a result of cirrhosis, the use of drugs (e.g. prednisolone), or the cause of the disease (e.g. alcohol), many patients are already biologically old and suffer from more extrahepatic disease than age controls at the time of transplant. After transplantation, the continuous use of immunosuppressive drugs adds especially to cardiovascular and cancer risk. Although the aim of liver transplantation is to reach long-term survival well beyond 15 years, especially in the younger age group, many do not reach this goal. On the other hand, taking into account all the risks for hepatic and extrahepatic disease one might fear that the quality of life and the overall health status of the long-term survivors is much less than optimal. Liver transplantation was started in our centre as early as 1979 as the fourth regular programme in the world. We evaluated the clinical outcome of patients surviving longer than 15 years, with special interest for the broad range of comorbidity and the self-perceived quality of life. Reports on this subject have been scarce so far [1,2].

The five-year survival of patients still alive 15 years after transplantation was 78%, with cardiovascular disease as the principle cause of death. It is interesting to note that even after 15 years, age was still not a prognostic marker for survival, and death was determined by comorbidity.

Comorbidity in the currently surviving patients, as listed in *figure* 1, consisted mainly of overweight, hypertension, cardiovascular disease, diabetes mellitus, osteoporosis, and *de novo* cancer. Renal insufficiency defined as clearance <50 ml/min was present in 11% of patients. Looking at this spectrum, two things are remarkable. First, although we did not compare the patient group with a gender- and age-matched control group, comparison with prevalence data in the Dutch population shows lower percentages in the general population [7-10]. From other studies, which focussed on one particular complication, we know that cardiovascular disease and cancer occur more often in organ transplant recipients than in controls [11-15]. Second, the spectrum of comorbidity we found appears to differ from that reported in the studies of Kisilisik *et al.* [1] and Cicarelli *et al.* [2] in patients surviving more than 10 years after transplantation. Our patients more often suffered from osteoporosis (prevalence 49 *vs.* 4 and 9%, respectively), skin cancer (32 *vs.* 4 and 7%), overweight (56 *vs.* 49 and 13%), and

cataract (24 *vs.* unknown and 8%). However, we less often observed hypertension (38 *vs.* 64 and 48%), and end-stage renal disease for which hemodialysis or renal transplantation was indicated (0 *vs.* 4 and 9%), and serum creatinine levels were significantly lower in our patient group.

Most likely, these differences in comorbid conditions reflect the different immunosuppressive regimens that were used in these patient cohorts. In the early years of our programme, patients were only taking prednisolone and azathioprine. Prednisolone was given in dosages that are, by today's standards, excessively high. A minority of patients started on cyclosporine-based triple therapy, but cyclosporine was tapered and discontinued after the second or third year in most patients. As a result, most of our long-term survivors are still treated with prednisolone and azathioprine. In contrast, Kizilisik *et al.*[1] have used cyclosporine, in combination with low-dose steroids, in most patients, and azathioprine in a minority of them. Cicarelli *et al.* [2] have used cyclosporine or tacrolimus in almost all patients, with prednisolone and/or azathioprine in some patients. The high prevalence of osteoporosis, cataract and overweight in our patients may well be the result of the continued use and high cumulative doses of steroids. Skin cancer might relate to the long-term use of especially azathioprine[16-18]. On the other hand, the limited and short-term use of calcineurin blockers in our patients seems to have led to a lower rate of hypertension and a virtual absence of renal insufficiency in comparison to the other groups. This underscores the importance of the immunosuppressive regimen as a determinant of future complications.

In earlier studies, including the patients presented in this study, we have shown that bone loss occurred mainly in the first year after transplantation, despite the preventive use of daily 1-alpha-hydroxycholecalciferol and 1 gram calcium, with no significant deterioration or even improvement afterwards [19,20]. In the present era development of osteoporosis before and after transplantation is a less serious problem due to preventive strategies with biphosphonates, which became available in the 1990s, in combination with calcium and vitamin D [21].

A second important finding concerns the graft. In total, 22% of our patients received a retransplant. We have previously reported that the cumulative retransplantation rate rises from 10% at one year to 22% at 15 years after the first transplantation. This figure does not differ from most centres [22]. It shows that retransplantation is feasible with good outcome. Currently, compensated cirrhosis is present in 11% of patients, but overall liver function is good. Recurrence of disease without major consequences as yet was found in a minority of patients transplanted for primary biliary cirrhosis, primary sclerosing cholangitis, and hepatitis C, as expected.

A third important finding concerns quality of life. We found that the patients generally were satisfied with their present health status, rating it on average as 7 on a scale of 0-10 (with 0 as lowest and 10 as optimal). However, as measured by the EQ-6D, about half of the patients reported limitations in the domains mobility, usual activities, and pain/discomfort. In addition a minority reports some anxiety or depression. In a study of Hoeymans *et al.* [23], Dutch adults in the general population scored better on all EQ-6D domains. Our findings seem to be in agreement with those from other centres.

In general, quality of life has been shown to improve after a successful transplantation, but in the long run remains lower than that of the general population[24-28]. Kizilisik et al.[1] report an equal or even better quality of life in comparison to age-matched controls, but they restricted their questionnaire to a self-perceived health score, satisfaction with life, self care, and activity level. Also our patients scored high on satisfaction and self care, but probably lower on activity level.
Quality of life as measured by the EQ-6D did not relate to the level of comorbidity as measured by the CCI. However, caution is warranted here because the CCI and its variants were originally developed and used for prediction of outcome after breast cancer [5], lung cancer [6], peritoneal dialysis [29], kidney transplantation [30], and other [31,32]. Caution is also called for with respect to the value of these self-assessments. Having been chronically ill, patients may accept physical problems without complaining. Many patients are grateful that they received this opportunity for survival, and tend to regard remaining problems as "minor".
To conclude, our data show that patients ultimately have to pay a price for long-term immunosuppression. Several strategies may be useful to keep this price as low as possible. Nowadays, the availability of a wide spectrum of immunosuppressive agents allows individualised selection of drugs, thereby avoiding specific side effects. Knowledge of regimen-specific long-term toxicities should prompt adequate monitoring for side effects and timely adaptation of the regimen, and the use of prophylactic measures (e.g biphosphonates, lipid lowering drugs). In this way, we may achieve a better long-term health status in future patients.

REFERENCES

1. Kizilisik AT, Grewal HP, Shokouh-Amiri MH, Vera SR, Hathaway DK, Gaber AO. Impact of long-term immunosuppressive therapy on psychosocial and physical well being in liver transplant recipients. Prog Transplant 2003;13:278-83.
2. Ciccarelli O, Kaczmarek B, Roggen F, et al. Long-term medical complications and quality of life in adult recipients surviving 10 years or more after liver transplantation. Acta Gastroenterol Belg 2005;68:323-30.
3. EuroQol Group. EuroQol – a new facility for the measurement of health-related quality of life. Health Policy 1990;16:199-208.
4. Krabbe PFM, Stouthard MEA, Essink-Bot ML, Bonsel GJ. The effect of adding a cognitive dimension to the EuroQol multiattribute health-status classification system. J Clin Epidemiol 1999;52:292-301.
5. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chron Disease 1987;40:373-83.
6. Birim O, Kappetein AP, Bogers AJJC. Charlson comorbidity index as a predictor of long-term outcome after surgery of non small cell lung cancer. Eur J Cardiothorac Surg 2005;28:759-62.
7. Website CBS (Central Bureau for Statistics): http://statline.cbs.nl
8. Website MLDS (Maag Lever Darm Stichting): http://www.mlds.nl
9. Website RIVM Nationaal Kompas Volksgezondheid : http://www.nationaalkompas.nl
10. Website College voor Zorgverzekeringen – GIPdatabank (Drug Information System of the Health Care Insurance Board): http://www.gipdatabank.nl

11. Therapondos G, Flapan A, Plevris J, Hayes P. Cardiac morbidity and mortality related to orthotopic liver transplantation. Liver Transpl 2004;10:1441-53.
12. Guckelberger O, Bechstein W, Neuhaus R, et al. Cardiovascular risk factors in long-term follow-up after orthotopic liver transplantation. Clin Transplant 1997;11:60-5.
13. Johnston S, Morris J, Cramb R, Gunson B, Neuberger J. Cardiovascular morbidity and mortality after orthotopic liver transplantation. Transplantation 2002;73:901-6.
14. Vallejo GH, Romero CJ, de Vicente JC. Incidence and risk factors for cancer after liver transplantation. Crit Rev Oncol Hematol 2005;56:87-99.
15. Haagsma EB, Hagens VE, Schaapveld M, et al. Increased cancer risk after liver transplantation: a population-based study. J Hepatol 2001;34:84-91.
16. Otley CC, Pittelkow MR. Skin cancer in liver transplant recipients. LiverTranspl 2000;6:253-62.
17. Parrish JA. Immunosuppression, skin cancer, and ultraviolet A radiation. N Engl J Med 2005;353:2712-3.
18. Kelley GE, Meikle W, Sheil AG. Effects of immunosuppressive therapy on the induction of skin tumors by ultraviolet irradiation in hairless mice. Transplantation 1987;44:429-34.
19. Haagsma EB, Thijn CJP, Post JG, et al. Bone disease after orthotopic liver transplantation. J Hepatol 1988;6:94-100.
20. Hamburg SM, Piers DA, van den Berg AP, et al. Bone mineral density in the long-term after liver transplantation. Osteoporos Int 2000;11:600-6.
21. Millonig G, Graziadei IW, Eichker D, et al. Alendronate in combination with calcium and vitamin D prevents bone loss after orthotopic liver transplantation: a prospective single-center study. Liver Transpl 2005;11:960-6.
22. Postma R, Haagsma EB, Peeters PM, Van den Berg AP, Slooff MJH. Retransplantation of the liver in adults: outcome and predictive factors for survival. Transpl Int 2004;17:234-40.
23. Hoeymans N, Van Lindert H, Westert GP. The health status of the Dutch population as assessed by the EQ-6D. Qual Life Res 2005;14:655-63.
24. Taylor R, Franck LA, Fibson F, Ddhwan A. A critical review of the health-related quality of life of children and adolescents after liver transplantation. LiverTranspl 2005;11:51-60.
25. Lewis MB, Howdle PD. Cognitive dysfunction and health-related quality of life in long-term liver transplant survivors. LiverTranspl 2003;9:1145-8.
26. Aadahl M, Hansen BA, Kirkegaard P, Groenvold M. Fatigue and physical function after orthopic liver transplantation. Liver Transpl 2002;8:251-9.
27. Bryan S, Ratcliffe J, Neuberger JM, Burroughs AK, Gunson BK, Buxton MJ. Health-related quality of life following liver transplantation. Qual Life Res 1998;7:115-20.
28. Hellgren A, Berglund B, Gunnarsson U, Hansson K, Norberg U, Bäckman L. Health- related quality of life after liver transplantation. Liver Transpl and Surg 1998;4:215-21.
29. Fried L, Bernadini J, Piranoino B. Charlson comorbidity index as a predictor of outcomes in incidental peritoneal dialysis patients. Am J Kidney Disease 2001;37:337-42.
30. Wu C, Evans I, Joseph R, et al. Comorbid conditions in kidney transplantation: association with graft and patient survival. J Am Soc Nephrol 2005;16:3437-44.
31. Nuttall M, Van der Meulen J, Emberton M. Charlson scores based on ICD-10 administrative data were valid in assessing comorbidity in patients undergoing urological cancer surgery. J Clin Epidemiology 2006;59:265-73.
32. Schroeder RA, Marroquin CE, Bute BP, et al. Predictive indices of morbidity and mortality after liver resection. Annals of Surgery 2006; 243: 373-9.

CHAPTER

7

Quality of life in patients with familial amyloidotic polyneuropathy long-term after liver transplantation

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ABSTRACT

Liver transplantation aims to halt progression of the disease in patients with familial amyloidotic polyneuropathy (FAP) caused by hereditary transthyretin-related (ATTR) amyloidosis. Insight in health-related quality of life of these transplanted patients with FAP can be of help to optimize health care delivery. The aim of this cross-sectional study was to assess the health-related quality of life of patients with FAP long-term after transplantation.

Nine patients with a post-transplant follow-up of 4 years or more were included in the study. During the annual checks, health-related quality of life was measured with the Short Form-36 (SF-36). Data were compared with non-FAP transplanted patients with the same duration of follow-up and with the normal Dutch population. Pre-transplant, all patients had signs of mild to moderate peripheral polyneuropathy.

The results showed that in patients with FAP health-related quality of life was stable in the first 4 years after transplantation. The domain of physical well-being at 4 years after transplantation was significantly lower compared to non-FAP transplanted patients and control Dutch population. The domain of emotional well-being was comparable with non-FAP controls. However, on most health areas the patients with FAP scored lower than the non-FAP transplanted patients and the Dutch controls. After four years, the three patients with FAP with longest follow-up (9-12 years) deteriorated in all health domains, except in self-perceived mental health.

This study, including only a small number of patients with FAP, shows a relatively low health-related quality of life after liver transplantation, which may deteriorate further with longer follow-up.

INTRODUCTION

Liver transplantation is the accepted treatment for patients with familial amyloidotic polyneuropathy (FAP) caused by hereditary transthyretin-related (ATTR) amyloidosis and has been performed since the beginning of the 1990s [1-6]. Hereditary ATTR amyloidosis is an adult-onset autosomal dominant fatal disorder with amyloid deposition in various tissues [7] and varies for the more than 100 different mutations of transthyretin (TTR) [8-10]. Main symptoms are progressive sensory motor peripheral polyneuropathy and autonomic neuropathy with e.g. constipation, diarrhoea, orthostatic hypotension, neuropathic joint destruction (Charcot joint), impotence in men, bladder retention, and other symptoms are related to affected visceral organs such as the gastrointestinal tract, heart and kidneys [5, 8, 10,11]. Liver transplantation in patients with FAP aims to halt the progression of the disease as the liver is the main organ producing TTR [2,4]. Apart from the liver, TTR is also produced by the retina and choroid plexus [4,11] which can cause ocular and meningeal deposition of amyloid, respectively. Preferably, liver transplantation for FAP has to be performed in the early stage of the disease as symptoms that are present before transplantation most often remain present thereafter. Ocular disease may progress as mutant TTR production outside the liver continues [3-6,9,11-14]. More than 1200 liver transplantations have been performed worldwide in 17 countries [5,15].

Evaluation of the results of transplantation for treatment of FAP-disease should include health-related quality of life to get a complete picture of the psychosocial impact of this disease after transplantation. It may also help to develop tools for patient education, counselling and organization of care [16,17]. Few publications describe about the quality of life of patients with FAP after liver transplantation. All publications on this subject originate from Sweden [1,17-20] which has an endemic area of FAP in the Umeå district. In the Swedish study, a disease-specific questionnaire was used that had been adapted from quality of life research of patients undergoing chemotherapy[18]. These Swedish studies describe the health-related quality of life of patients with FAP with a short follow-up duration of median 1 and 2 years after transplantation [1,18].

The aim of the present study was to assess the health-related quality of life as measured by the Medical Outcome Study 36-item Short Form Survey (SF-36) of patients with FAP, long-term after orthotopic liver transplantation.

PATIENTS AND METHODS

Between August 1995 and January 2004, 13 patients with FAP underwent a liver transplantation at our hospital. After transplantation, all patients had annual checks for FAP-related disease. Severity of disease-related signs and symptoms as well as monitoring of improvement, stabilization, and progression were assessed yearly and reported to the Familial Amyloidotic Polyneuropathy World Transplant Registry [15]. For the present study, demographic and disease-related characteristics were derived from the medical files. Included in the present study were the nine patients with a follow-up of 4 years or more after transplantation, per January 2008. Four patients died within 2 years after transplantation and were excluded; two patients died perioperatively because of amyloid-related cardiovascular death, one patient died of septicaemia, and one patient died of the sequelae of acute pancreatitis.

General health status

During the annual checks, quality of life was measured by the Medical Outcome Study 36-item Short Form Survey (SF-36) [21,22]. SF-36 is a standardized, self-administered questionnaire measuring health-related quality of life as defined in the constitution of the WHO [23]. The SF-36 was constructed to measure eight health areas using multi-item Likert scales containing 2-10 items each. One separate item, Health Transition, gives a rating of health now compared to 1 year ago. Most of the other items ask the patient to look back 4 weeks. The eight health areas are: physical functioning (PF), role limitations due to physical problems (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role limitations due to emotional problems (RE), and mental health (MH). The health areas of PF, RP, and BP relate to physical well-being, whereas the health areas of SF, RE, and MH relate to emotional well-being. GH and VT are related to both physical and emotional well-being. The scale scores on the health areas are the sum of the scores per item transformed to a scale of 0-100. The scales are constructed in such a way that a higher score signifies a better health.

Controls and comparison

First, the SF-36 scores of the patients with FAP at 4 years after transplantation will be compared with a non-FAP liver transplant group. Previously we studied medication compliance in 123 liver transplant recipients. This concerned a cross-sectional study, and included 16 patients at 4 years after transplantation [24]. The SF-36 data of these patients are so far unpublished. The characteristics of the 16 patients, measured at 4 years after transplantation are: 8 females, and age median 45 years (range 24-63). Their pre-transplant diagnosis were primary sclerosing cholangitis in six patients, cryptogenic cirrhosis in three patients, primary biliary cirrhosis in two patients, auto-immune cirrhosis in two patients and other diagnosis in three patients.

Second, the SF-36 scores of the patients with FAP at 4 years after transplantation will be compared with the SF-36 scores of a normal Dutch population (n = 1617, 65% men, age 16-75 years) [25]. Neither of the control groups was age matched with the FAP study group.

Statistics

Statistical analysis was performed using the Statistical Package for the Social Sciences 14.0 (SPSS Inc., Chicago, IL, USA). Data were checked for normality. Mean, standard deviation, median and ranges were calculated as appropriate. For a two-group comparison the Wilcoxon signed-ranks test was used and the Friedman test for comparing more than two groups. A $p \leq 0.05$ was considered to indicate statistical significance.

To explore whether the mean scores of the study group and the control normal Dutch population differed significantly on the health areas, the Standard Error (SE=sd/√n) of the mean score of the study group was computed and used for comparison. A difference of ± 2 SE between the mean score of the study group and the mean score of the Dutch population indicated statistical significance.

RESULTS

Patient characteristics

The characteristics of the nine patients with FAP are listed in Table I. The median age at liver transplantation was 52 years (range 35 – 58 years). Time from onset of FAP through transplantation was median 2 years (range 7– 42 months). The pre-transplant clinical symptoms of FAP are shown in Figure 1. All patients had signs of mild to moderate peripheral polyneuropathy. Other symptoms of FAP were mainly related to the digestive tract, cardiovascular and urinary tract. The median modified body mass index was 1004 kg m^{-2} g l^{-1} (range 761-1228). The median duration of follow-up after transplantation was 6 years (range 4-12 years). Progression of the clinical symptoms at 4 years after transplantation is shown in Figure 2. A substantial minority

Table I. Patient characteristics (n=9)

Patient number	Gender	TTR-mutation	Duration of FAP-symptoms before LT (months)	Age at LT (yrs)	Duration of follow-up after LT (years)
1	F	Tyr 114 Cys	24	49	9 * †
2	M	Tyr 114 Cys	36	46	12
3	F	Val 30 Met	29	35	10
4	F	Val 30 Met	7	46	9
5	M	Val 30 Met	42	58	4 †
6	F	Tyr 114 Cys	36	54	4
7	M	Val 30 Met	17	53	6
8	F	Glu 47 Gly	16	52	5
9	F	Tyr 114 Cys	20	52	4

* follow-up with SF-36 only possible until 6 years after liver transplantation due to progressive FAP-disease. † death.

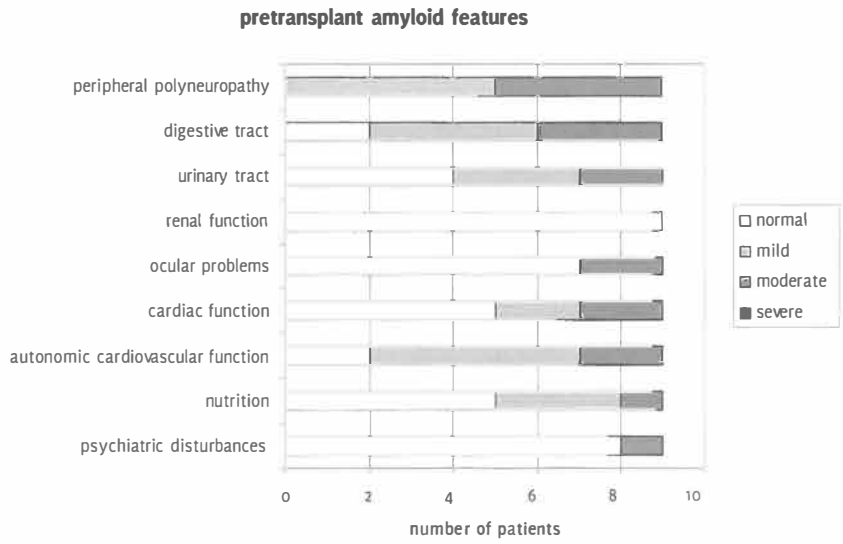

Figure 1: The pretransplant clinical symptoms of the study group, semi-quantitatively.

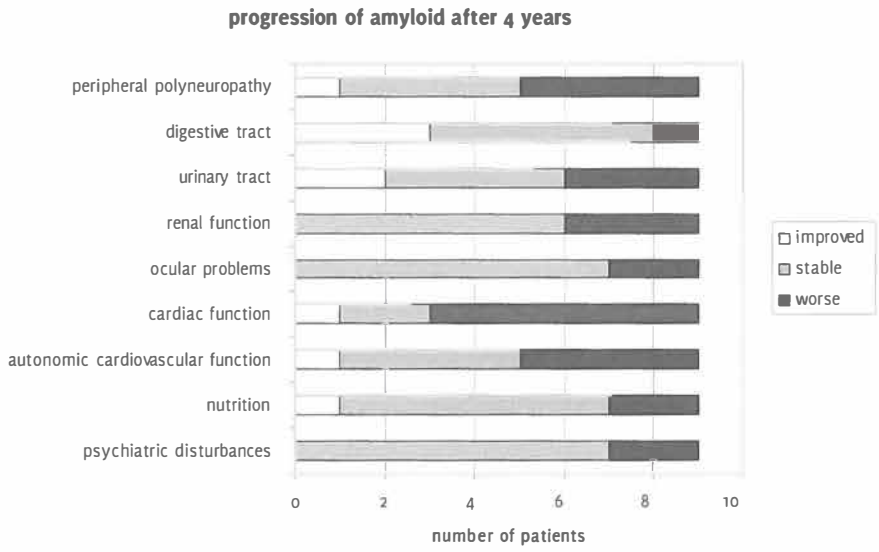

Figure 2: Change in symptoms at 4 years after liver transplantation.

of patients developed progression of disease. Most problematic was a decrease in cardiac function, which occurred in six of the nine patients. Two patients died, 9.8 and 4.5 years after transplantation, respectively. In both patients death was related to end-stage FAP.

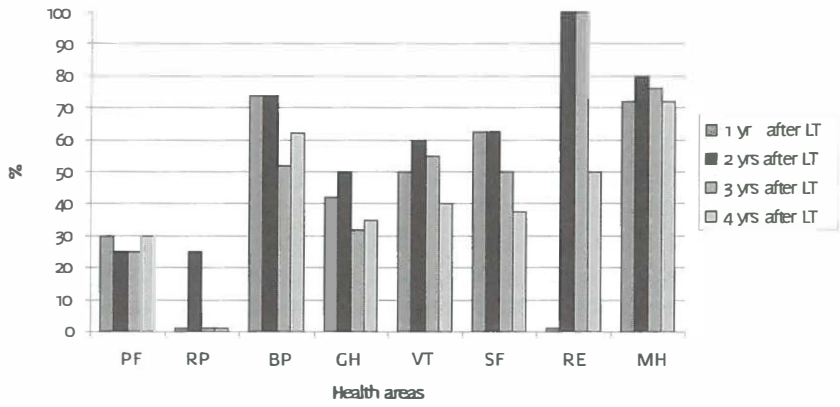

Figure 3: Median scores on SF-36 health areas at 1, 2, 3 and 4 years after liver transplantation (n=9).

The first four years after liver transplantation

Reported health transition. At the first year after transplantation, two of the nine patients reported that their general health improved somewhat compared to 1 year ago, and for two patients it was unchanged. Four patients reported their health was somewhat worse and one patient reported that it was much worse 1 year after transplantation. At 2 years, little improvement is reported by seven patients, and two patients reported a somewhat worse health state. After 2 years an overall deterioration was reported. At 3 years, three patients reported their health somewhat worse and two patients reported that it was much worse. At 4 years, six patients reported a somewhat worsened health, and one patient reported a much worsened health. Improvement was not reported anymore.

Scores on health areas. The scores on the eight health areas in the first 4 years after transplantation are summarized in Figure 3. No statistical significant differences were found among the years. Below data are given in medians with ranges in brackets.

Physical Functioning. During the years PF is stable, but quite low with a score of 25-30%. The ranges between 0 and 95% are wide however. PF reflects limitations in performing daily activities ranging from vigorous activities, such as running and lifting heavy objects to moderate activities as walking and bathing oneself.

Role Physical. The scores on this health area are also very low (median 0-20%). Again the ranges are wide (0-100). The low scores indicate that the patients have serious limitations performing their daily activities, e.g. 'cut down the amount of time spent on work or other activities' and 'accomplished less than would like'.

Bodily Pain. Pain clearly interferes with normal life in a substantial number of patients, and BP seems to increase during the years. The BP score was 74% (12-100) at 1 year, 74% (0-100) at 2 years, 52% (10-100) at 3 years, 62 % (12-100) at 4 years after transplantation.

General Health. Within the GH items patients have to rate their health ranging from 'excellent to poor', compare their health with others they know, and give their opinion on their

future health development. GH was scored quite low. At 1 year the GH score was 42% (10-67), at 2 years 50% (15-60), at 3 years 32% (5–82) and at 4 years 35% (5-72). Again the ranges are wide.

Vitality. The VT score in the first 3 years was rather stable with scores of 50% (10-85%), 60% (10-85), and 55% (15-90) respectively. A decrease to 40% (20-90) was reported in the fourth year. Vitality, being the item that reflects the amount of energy that people have in daily life, thus seems to vary widely between the patients.

Social Functioning. The extent and frequency of health problems interfering with social activities is scored with this health area. A gradual decrease seems to be present. The first 2 years the SF score was 62.5% (0-87.5). At the third and fourth year this decreased to 50% (0-100) and 37.5% (12.5-100), respectively.

Role-emotional. Emotional problems such as depressive feelings and anxiety and its influence on daily activities are scored with this health area. This health area showed ups and downs. At 1 year, the score was very low (0% (0-100)). A clear improvement to 100% (0-100) was reported at 2 and 3 years. At 4 years the score was lower again, 50% (0-100).

Mental Health. This health area scored quite high in most patients, especially compared to the other areas. And no deterioration was noted through the years. The score was 72% (36-92) at 1 year, 84% (48-88) at 2 years, 76% (36-92) at 3 years and 72% (36-96) at 4 years after transplantation.

Comparison with non-FAP liver transplant patients and the normal Dutch population

Comparison of the SF-36 scores of the patients with FAP with non-FAP patients, at 4 years after transplantation, showed that on all health areas, except RE, the patients with FAP scored significantly lower than the non-FAP patients (p values between 0.04 and 0.00).

Comparison of the patients with FAP with an average of the normal Dutch population

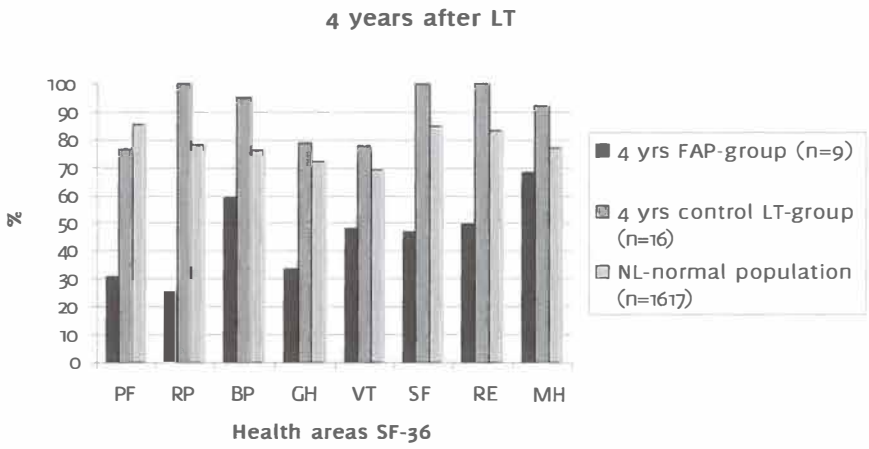

Figure 4. Comparison of mean SF-36 health area scores of the FAP-group with the non-FAP liver transplant (LT) group and normal Dutch (NL) population.

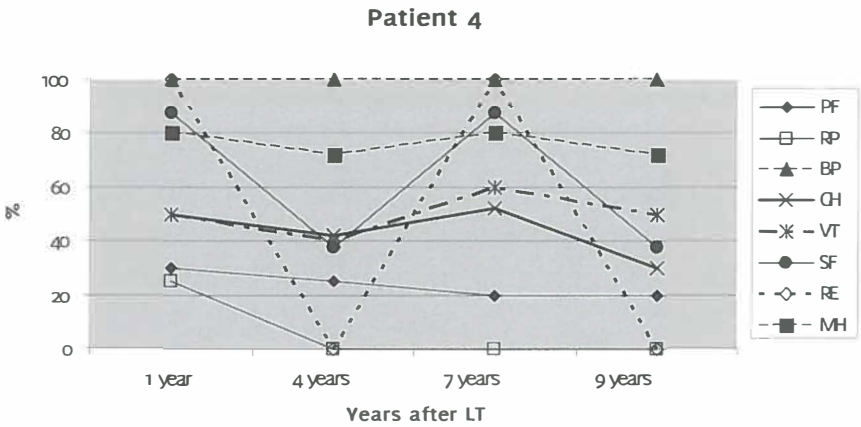

Figure 5. Median scores of patient 4 on SF-36 health areas at 1, 4, 7 and 9 years after liver transplantation.

revealed that patients with FAP scored significantly lower on five of the eight health areas, i.e. PF, RP, GH, VT, and SF. No differences were found for BP, RE and MH. The non-FAP transplanted patients scored almost similar to the Dutch control population. Figure 4 summarizes the data.

Long-term follow-up: case reports

Four of the nine patients included in this study had a long-term follow-up of 9 to12 years after transplantation. One of these patients, patient number 1, was bedridden, blind and deaf, for several years before she died 9.8 years after transplantation. From this patient long-term SF-36 data are not available. In the following, we will describe the data of the other three long-term patients.The data are shown in Figures 5-7. For clarity of presentation only the data of years 1, 4, 7, 9 or10 and 12 are depicted.

Follow-up 9 years: patient number 4. The SF-36 data are depicted in Figure 5. The scores go up and down through the years, especially for RE and SF, with low scores for RP and PF, and surprisingly high scores for BP, without a real decreasing trend. With respect to health transition: when asked to compare health with the situation one year ago, the patient reported it to be 'about the same' at 1, 2, 3, 7 and 8 years after transplantation, 'much better' at 5 years, 'much worse' at 6 years and 'somewhat worse' at 4 and 9 years after transplantation.

The main problem before transplantation was a moderate, mainly sensory polyneuropathy of her legs with recurrent pressure ulcers. After transplantation, this problem got worse with development of Charcot's joints of the feet. Recurrent ulcers with recurrent infections, including osteomyelitis caused many hospitalizations and three orthopaedic operations. Amyloid symptoms and signs otherwise remained stable and very mild through the years. The recurrent infections most likely explain the large variation in scores of the health areas.

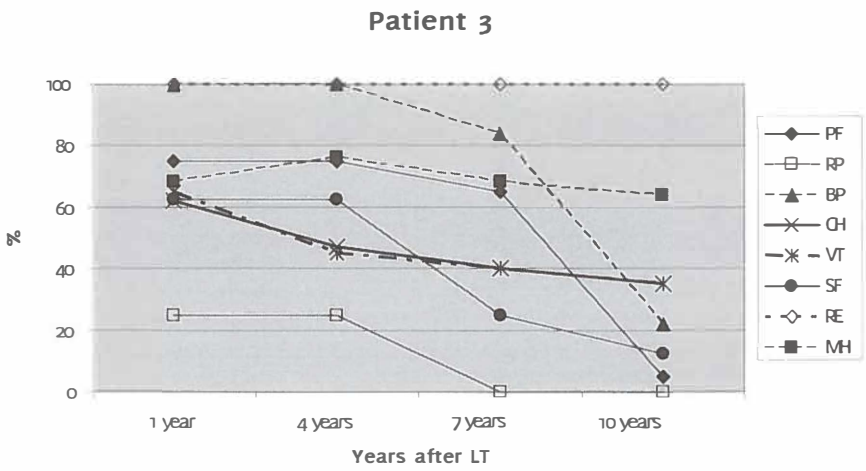

Figure 6. Median scores of patient 3 on SF-36 health areas at 1, 4, 7 and 10 years after liver transplantation.

Follow-up 10 years: patient number 3. The SF-36 data are depicted in Figure 6. One year after transplantation all health areas, except RP, are scored above 60%. After the fourth year, however, a progressive decline is noticed. At 10 years only RE and MH are still scored above 60%. This is reflected in the health transition: the patient reported it to be 'rather stable' to 'somewhat worse' in the first 5 years after transplantation, in the years thereafter 'somewhat worse' at 6, 8, and 9 years to 'much worse' at 7 and 10 years after transplantation.

Before transplantation this patient suffered already from moderate, mainly sensory polyneuropathy, mild autonomic cardiovascular dysfunction, and gastrointestinal motility disturbance. In the first 3 years after transplantation no progression was noted, but in the following years an increase of autonomic cardiovascular dysfunction with hypotension and hypertension occurred, together with an increase of polyneuropathy and development of recurrent urinary tract infections related to bladder dysfunction. She suffered from serious migraine, and after 6.5 years an intracerebral bleeding occurred, after which cognitive functions also mildly declined. A pacemaker was necessary after 7.5 years. Presently she suffers mainly from fatigue, polyneuropathy, severe migraine, serious orthostasis, and weight loss.

It says something about her mental power that despite this declining clinical course she still scored quite high for RE and MH after 10 years. Of the three long-term patients she scores the lowest on most health areas at the end of follow-up.

Follow-up 12 years: patient number 2. The SF-36 data are depicted in Figure 7. The first 4 years showed rather stable scores. The patient scored low mainly for BP and GH. Hereafter a decline is seen, with a somewhat fluctuating course. At 12 years all scores are low except for MH. Physical well-being scores lower than emotional well-being.

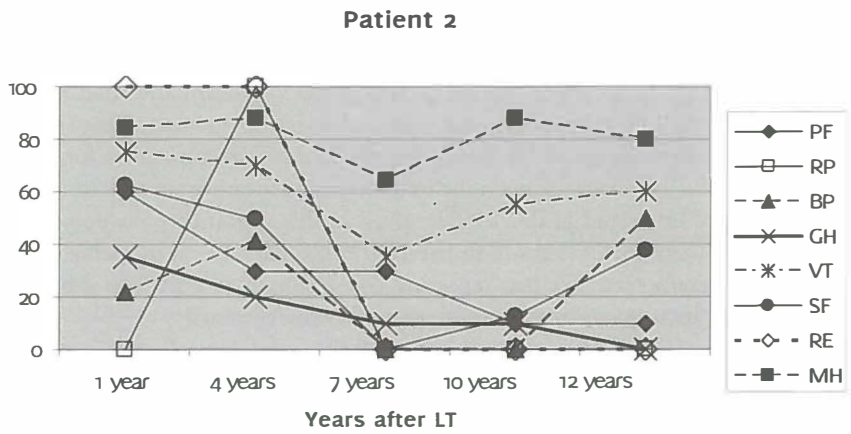

Figure 7. Median scores of patient 2 on SF-36 health areas at 1, 4, 7, 10 and 12 years after liver transplantation.

With respect to health transition: the first 8 years after transplantation the patient reported health compared with 1 year ago as 'somewhat worse now' and 'about the same'. At 9 and 10 years, it was 'much worse' compared with one year ago and only 'somewhat worse' at 11 and 12 years after transplantation.

Before transplantation this patient suffered already from moderate, mainly sensory polyneuropathy with pain, mild gastrointestinal motility disorder and mild bladder dysfunction. The first 4 years showed no progression of amyloid features, but the patient burnt his left foot, later fractured his left ankle at 3 years, and developed Charcot's joints of his feet. Hereafter amyloid features were slowly progressive. Progressive vitreous opacities developed after 5 years, migraine, transient ischemic attacks, and weight loss after 8 years, feet ulcers after 9 years, memory complaints, deafness and urinary tract infections after 10 years. In addition there were two episodes of cholestasis in relation to a stenosis of the duct-duct bile duct anatomosis for which endoscopic treatment was needed at 5.5 and 10.5 years after transplantation. This clinical course of progressive amyloid seems reflected in the SF-36 data.

DISCUSSION

In the present study, the focus was on quality of life long-term after transplantation for patients with FAP. Patients may die earlier after transplantation, either related to FAP or to the transplantation (or both), but the aim of transplantation for FAP is to halt amyloid disease progression on the long-term and improve survival time, and we therefore were interested in the self-perceived health and quality of life of patients who reached their goal of long-term survival. Published data on this subject are not many, and therefore we felt that reporting our results is worthwhile although the number of patients transplanted in our center is relatively small.

As in other centers, the first patients with FAP that were transplanted in our center showed more advanced disease than later patients. Although in all patients the modified body mass index was still within normal ranges. Presently, we aim to transplant in an early stage of disease, although due also to waiting times for a suitable donor, this still is not always possible.

The study group presented showed, in general, mild to moderate FAP disease before the transplantation. In judging the data it should be noted that only four of the nine patients had the variant TTR with the world wide most common mutation Val30Met. It has been shown that progression of disease, also after transplantation, may be more serious in several non-Val30Met patients with FAP [2,5,10,14,26].

In the first 4 years, we found that the scores on physical well-being were quite low but stable, despite the clinical finding that the disease had progressed in some patients. The patients with FAP scored significantly lower, however, than non-FAP liver recipients and than Dutch population controls. Keeping in mind that the comparison has its limitations as the control groups were not age matched, this finding is not surprising as the patients keep the symptoms of their amyloidosis. It illustrates that successful transplantation in a patient with FAP is only a relative success compared to transplantation in a patient with a cirrhotic liver.

In the first 4 years, the scores on emotional well-being were higher than on physical health. And in contrast to physical well-being, for emotional well-being the differences with non-FAP liver recipients and Dutch population controls were only small. Emotional well-being is covered by the health areas of social functioning, role-emotional aspects and mental health, and the relatively good score corresponds with our experiences with this group of patients. Most of the patients have tremendous social support of partner and next of kin. The finding is consistent with other studies[17,18]. Jonsén measured health-related quality of life in Swedish patients, and it was found that the majority of 12 patients were satisfied with the outcome of transplantation without relation to existing symptoms of FAP. She also found that quality of life was primarily related to neurological impairment of the upper extremities, especially hand function [18], although hope and expectation after a successful transplantation often was replaced by a feeling of disappointment and 'bad' quality of life by ongoing disease later on [16].

We report the self-perceived quality of life in three patients with longest follow-up between 9 and 12 years. In all three patients physical health deteriorates, which is also

reflected in deteriorating scores on emotional well-being although the score on the item mental health remains relatively high. The course of quality of life in these three patients confirms the clinical findings of increasing amyloid-related complications after the rather stable first 4 years. Although it has been shown that progression of disease may be absent in patients transplanted for Val30Met with mild symptoms [6,11,27], this often is not the case for other variants, regrettably [2,5,10,14,26]. Amyloid formation may continue based on variant TTR production in the retina and choroid plexus, and based on wild type TTR deposited on pre-existing amyloid [6,8,28].

From the present study cannot be derived that liver transplantation has been of much benefit to the patients in physical or mental respect, as the number of patients that are included in the study is too small. It gives rise to worries however, especially for patients with non-Val30Met TTR variants. It is important, however, to have found that the patients are mentally strong despite worsening physical well-being. This is also known from quality of life studies in other transplant patients. Liver transplant recipients accept limitations and they are more easily satisfied with the life they have compared to healthy controls [29]. In this view, most patients with FAP are fully aware of the evolution of FAP without transplantation as they have seen the course in close relatives before the era of transplantation [18,19].

A limitation of the present study may be that the SF-36 is a generic instrument and not disease-specific and that it may not be sensitive enough to detect small changes in the health-related quality of life of these patients. Together with the small number of patients this is probably the reason that there was minor differentiation in the health areas of '*Role-emotional*' and '*Role-physical*'. These health areas consist of three and four items respectively. There were two scoring possibilities of '*yes or no*' and the majority of the patients answered all items with 'yes' or all items with 'no', so transformation of this scores to a 0-100 scale resulted in a score of zero or in a score of 100. Furthermore the SF-36 lacks an overall score and does not assess cognitive functioning [30]. Advantage of the SF-36 in our group was that it enabled us to compare the data with non-FAP liver transplant patients [24,30] and Dutch population controls.

In conclusion, the present study that included a relatively small number of patients transplanted for FAP, showed that self perceived quality of life as measured with the SF-36 was stable in the first 4 years after liver transplantation, but in the domains for physical well-being was significantly lower compared to non-FAP liver transplant patients and a control Dutch population. In some aspects, emotional well-being was comparable to non-FAP controls. The few patients with longer follow-up deteriorated in all domains, except in self-perceived mental health. The small number of patients being the major limitation of the study, quality of life studies in much larger patient populations with different TTR variants and longer follow-up are needed to get a better understanding in the course of FAP after liver transplantation.

REFERENCES

1. Jonsén E, Athlin E, Suhr O. Familial amyloidotic patients' experience of the disease and of liver transplantation. J Adv Nurs 1998;27:52-58.
2. Suhr OB, Herlenius G, Friman S, Ericzon BG. Liver transplantation for hereditary transthyretin amyloidosis. Liver Transpl 2000;6:263-276.
3. Suhr OB, Ericzon B-G, Friman S. Long-term follow-up of survival of liver transplant recipients with Familial Amyloid Polyneuropathy (Portuguese type). Liver Transpl 2002;8:787-794.
4. Suhr OB. Impact of liver transplantation on familial amyloidotic polyneuropathy (FAP) patients' symptoms and complications. Amyloid: Int J Exp Clin Invest 2003;10 Suppl 1:77-83.
5. Herlenius G, Wilczek HE, Larsson M, Ericzon BG. Ten years of international experience with liver transplantation for familial amyloidotic polyneuropathy: results from the Familial Amyloidotic Polyneuropathy World Transplant Registry. Transplantation 2004;77:64-71.
6. Suhr OB, Friman S, Ericzon BG. Early liver transplantation improves familial amyloidotic polyneuropathy patients' survival. Amyloid: J Protein Folding Disord 2005;12:233-238.
7. Andrade C. A peculiar form of peripheral neuropathy. Familial atypical generalised amyloidosis with special involvement of the peripheral nerves. Brain 1952; 75:408-427.
8. Benson MD. The hereditary amyloidosis. Best Pract & Res Clin Rheum 2003;17: 909-927.
9. Ando Y. Liver transplantation and new therapeutic approaches for familial amyloidotic polyneuropathy (FAP). Med Mol Morphol 2005;38:142-154
10. Benson MD, Kincaid JC. The molecular biology and clinical features of amyloid neuropathy. Muscle & Nerve 2007;36:411-423.
11. Yamamoto S, Wilczek HE, Nowak G, Larsson M, Oksanen A, Iwata T, Gjertsen H, Söderdahl G, Wikström L, Ando Y, Suhr OB, Ericzon BG. Liver transplantation for familial amyloidotic polyneuropathy (FAP): a single-center experience over 16 years. Am J Transplant 2007;7: 2597-2604.
12. Adams D, Samule D, Goulon-Goeau C, Nakazato M, Costa PMP, Feray C, Planté V, Ducot B, et al. The course and prognostic factors of familial amyloid polyneuropathy after liver transplantation. Brain 2000;123:1495-1504.
13. Perdigoto R, Furtado AL, Furtado E, Oliveira FJ, Geraldes B, Mota O, Tome L, Viana J. The Coimbra University Hospital experience in liver transplantation in patients with familial amyloidotic polyneuropathy. Transpl Proc 2003:35;1125.
14. Stangou AJ, Hawkins PN. Liver transplantation in transthyretin-related familial amyloid polyneuropathy. Curr Op Neur 2004;17;615-620.
15. Familial Amyloidotic Polyneuropathy World Transplant Registry. Available from: http://www.fapwtr.org.
16. Jonsén E. Liver transplantation in Familial Amyloidotic Polyneuropathy-the Bright and the Dark side[dissertation]. Umeå: Umeå University, Sweden;1999. Available from Umeå University, New series No 610.
17. Jonsén E, Athlin E, Suhr OB. Family members' experience of familial amyloidotic polyneuropathy-an infernal struggle and a fact of live. J Adv Nurs 2000;31:347-353.
18. Jonsén E, Suhr O, Athlin E, Wikström L. Quality of life after liver transplantation in patients with familial amyloidotic polyneuropathy. Amyloid: Int J Exp Clin Invest 1996;3:124-129.
19. Jonsén E, Athlin E, Suhr O. Familial amyloidotic patients' experience of the disease and of liver transplantation. J Adv Nurs 1999;27:52-58.
20. Jonsén E, Suhr OB, Tashima K, Athlin E. Early liver transplantation is essential for familial amyloidotic polyneuropathy patients' quality of life. Amyloid: J Protein Folding Disord 2001;8:52-57.
21. Ware JE, Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36): I. Conceptual framework and item selection. Med Care 1992;30:473-483.
22. Van der Zee KI, Sanderman R, Heyink JW, et al. Psychometric qualities of the RAND-36-Item Health Survey 1.0: a multidimensional measure of general health status. Int J Behav Med 1996;3:104-122.

23. World Health Organization. Constitution of the World Health Organization. Basic Documents, Forty-fifth edition, Supplement, October 2006. Geneva, Switzerland.
24. Drent G, Haagsma EB, De Geest S, Berg van den AP, Ten Vergert EM, Bosch van den HJ, Slooff MJH, Kleibeuker JH. Prevalence of prednisolone (non)compliance in adult liver transplant recipients. Transpl Int 2005;18:960-966.
25. Aaronson NK, Muller M, Cohen PDA, Essink-Bot ML, Fekkes M, Sanderman R, Sprangers MAG, Velde te A, Verrips E. Transplantion, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. J Clin Epidemiol 1998;51:1055-1068.
26. Singer R, Mehrabi A, Schemmer P, Kashfi A, Hegenbart U, Goldschmidt H, et al. Indications for liver transplantation in patients with amyloidosis: A single center experience with 11 cases. Transplantation 2005;80:S156-S159.
27. Sharma P, Perri RE, Sirven JE, Zeldenrust SR, Brandhager DJ, Rosen CB, Douglas DD, Mulligan DC, et al. Outcome of liver transplantation for familial amyloidotic polyneuropathy. Liver Transpl 2003;9:1273-1280.
28. Haagsma EB, Gameren van II, Bijzet J, Posthumus MD, Hazenberg BPC. Familial amyloidotic polyneuropathy: long-term follow-up of abdominal fat tissue aspirate in patients with and without liver transplantation. Amyloid: J Protein Folding Disord 2007;14:221-226.
29. Dew MA, Switzer GE, Goycoolea JM, Allen AS, DiMartini A, Kormos RL, Griffith BP. Does transplantation produce quality of life benefits? Transplantation 1997;64:1261-1273.
30. Tome S, Wells JT, Said A, Lucey MR. Quality of life after liver transplantation. A systematic review. J Hepatol 2008;48:567-577.

CHAPTER 8

Summary and future perspectives

SUMMARY

Liver transplantation has been a treatment option for patients with end stage liver disease and for a selected group of patients with inborn metabolic disorders for several decades now. From the early years of liver transplantation to present the results have improved remarkably. Relatively little attention has been paid to the adult patient's experience of living with a liver transplant. Important interrelating issues in this respect are the patient's adherence to immunosuppressive drugs, the experienced side effects of immunosuppressive drugs, and the long-term health-related quality of life (HRQOL).

Chapter 1 provides a general introduction on liver transplantation and introduces the three topics of this thesis, namely medication nonadherence, symptom experience and long-term HRQOL.

In **Chapter 2** a review is presented of the literature that exists on symptom experience, medication nonadherence and long-term HRQOL in adult liver transplant recipients. Except for studies on quality of life it became clear that not much research has been conducted on symptom experience and medication nonadherence in adult liver transplant recipients. This is in contrast to the considerable number of studies in renal and heart transplant patients.

Six studies in adult liver transplant recipients have been retrieved that discuss symptom experience in their methodology and most of these studies were part of a study on HRQOL. It was shown that women experience more distress due to subjective side effects of drugs than men.

A total of 14 studies with the main focus on medication nonadherence were found. In most studies adherence was assessed as part of alcohol relapse studies and inadequate measurement methods of adherence were mostly used. Overall, medication nonadherence in adult liver transplant patients seems to be low, but when it occurs it can cause serious damage to the patient in terms of rejection, graft loss or even death. Important risk factors for nonadherence were found to be costs of drugs, age below 40 years, mental disease, side effects of drugs, beliefs that drugs were harmful, and a large influence of being a transplant patient on patient's life.

HRQOL has mainly been studied short term after liver transplantation. In general, in the first years after transplantation HRQOL was judged to be satisfactory, but below the level of the general population. Long-term results are less clear however.

Chapters 3 to 5 concern investigations performed in a study group of 123 adult liver transplant recipients.

In **Chapter 3** the results of a study into medication nonadherence (also called noncompliance) are presented. Limited evidence is available concerning noncompliance with the immunosuppressive regimen in adult liver transplant recipients. In our study we prospectively assessed prednisolone noncompliance in 108 adult liver transplant recipients using electronic event monitoring (EEM) in an outpatient setting. EEM is a pill bottle fitted with a cap containing a microelectronic circuit that registers date and time of bottle openings and closings. Median taking compliance was 100% (range 60 -105%), median dosing compliance was 99% (range 58-100%), median timing

compliance was 94% (42-100%). A drug holiday of ≥ 48 hours was found in 39% of the patients; of ≥72 hours in 16% of the patients. Using EEM in liver transplant recipients, we found an overall high level of compliance for prednisolone, except that timing compliance was low in about one third of the patients. Age below 40 years was found to be a significant risk factor for decreased timing compliance and for drug holidays of ≥ 48 hours.

There are limited data on the influence of medication noncompliance on clinical outcome. The aim of the study presented in **Chapter 4** was to investigate the influence of prednisolone noncompliance, as measured by EEM, on clinical outcome and costs during a follow-up period of two years in 108 adult liver transplant recipients.

Except for a somewhat higher alkaline phosphatase in patients who were least taking and dosing compliant and in those who had most drug holidays of at least 48 hours, we found no relationship between compliance parameters and liver tests, acute rejection episodes, prescribed tapering of immunosuppression, hospital admissions, and patient and graft survival during the two years of follow-up. It may be concluded that the level of prednisolone noncompliance of our liver transplant patients had no significant clinical relevance. This is in contrast to findings in adult renal and heart transplant recipients, in which minor deviations of dosing schedule were associated with poor clinical outcome. An explanation might be found in that the liver is considered to be a privileged organ in immunological terms. The level of non-compliance with immunosuppressive drugs at which clinical outcome deteriorates after liver transplantation remains to be elucidated in further studies.

Symptom experience (occurrence and perceived distress) associated with side effects of immunosuppressive medications may well be associated with medication non-compliance and decreased quality of life. The aims of the study presented in **Chapter 5** were: first, to assess symptom experience in clinically stable adult patients during long-term follow-up after liver transplantation; and second, to study the relationship between symptom experience and medication non-compliance. This cross-sectional study included 123 liver transplant patients. Symptom experience was assessed using the 'Modified Transplant Symptom Occurrence and Symptom Distress Scale' (29-item version) at the annual evaluation. According to the duration of follow-up, patients were divided into a short-term (1-4 years) and a long-term (5-18 years) cohort. Results showed that increased hair growth was the most frequent symptom in both sexes. Symptom distress was more serious in women than in men. The most distressing symptom in women was excessive and /or painful periods, and impotence in men. Clear differences were revealed at item level between symptom occurrence and symptom distress in relationship with the two time cohorts and between sexes. No relationship was found between symptom experience and prednisolone non-compliance as measured by EEM.

Chapters 6 and 7 concern investigations into the health status and quality of life in two well defined study groups.

Liver transplantation was started in our center as early as 1979. We were interested in the current health status of patients who have survived for more than 15 years after liver transplantation, with special interest for the broad range of comorbidity and

the self perceived quality of life. Results are presented in **Chapter 6**. All patients who underwent a liver transplantation at an adult age between March 1979 and February 1991, and who survived at least 15 years were eligible for the study. Data were collected from the medical records. Health-related quality of life was assessed using the Six-Dimensional EuroQol test. Thirty seven patients were alive at the time of the study with a median follow-up of 18.8 years (range 15.0-26.8) after transplantation. Comorbidity consisted predominantly of overweight (57%), osteoporosis (49%), de novo cancer (38%, mainly skin cancer), hypertension (38%), cardiovascular events (19%), diabetes mellitus (22%), cataract (24%), and renal clearance below 50 ml/min (11%). Eight patients (22%) underwent a re-transplantation, and compensated cirrhosis was present in 4 patients (11%). The pattern of comorbidity seemed to relate to the type of immunosuppression which consisted mainly of prednisolone and azathioprine. Quality of life was perceived as satisfactory (7 on a scale of 0 to10). However, about half of the patients reported limitations in the domains mobility, usual activities and pain/discomfort. In addition a minority reported some anxiety or depression. We conclude that the outcome of liver transplantation in this early cohort of patients is fairly good. Improvements may be achieved by adaptations in the immunosuppressive regimen.

Chapter 7 reports a study on HRQOL in patients transplanted because of familial amyloidotic polyneuropathy (FAP). FAP is an autosomal dominant inheriting disorder associated with mutations of the protein transthyretin, which is almost entirely produced in the liver. FAP characteristically presents with progressive peripheral and autonomic neuropathy, but cardiac amyloid is frequent and may dominate the clinical picture. Initially it was reported that liver transplantation resulted in overall improvement. However, it has become clear that in a substantial percentage of patients disease progression is not prevented in all organ systems. Insight in the HRQOL of these transplanted patients with FAP can be of help to optimize healthcare delivery. We performed a cross-sectional study to assess the HRQOL of patients with FAP long-term after transplantation.

Nine patients with a post-transplant follow-up of 4 years or more were included in the study. During the annual checks HRQOL was measured with the Short Form-36 (SF-36). Data were compared with non-FAP transplanted patients with the same duration of follow-up and with the normal Dutch population. Pre-transplant all patients had signs of mild to moderate peripheral polyneuropathy. The results showed that in patients with FAP HRQOL was stable in the first 4 years after transplantation. The domain of physical well-being at 4 years after transplantation was significantly lower compared to non-FAP transplanted patients and the normal Dutch population. The domain of emotional well-being was comparable to non-FAP controls. However, on most health areas the patients with FAP scored lower than the non-FAP transplanted patients and the Dutch controls. After 4 years the three patients with FAP with longest follow-up (9-12 years) deteriorated in all health domains, except in self-perceived mental health. This study which includes only a small number of patients with FAP shows a relatively low HRQOL after liver transplantation which may deteriorate further with longer follow-up.

FUTURE PERSPECTIVES

Knowledge about the impact of a liver transplantation on the life of the transplant patient enables the healthcare workers to support the patients in a meaningful way and to learn from the experiences of the patients.

Medication nonadherence has evolved in the last decade to a subject of utmost importance, internationally, and on a national scale. The Nonadherence Transplant Consensus Conference in Tampa (2008) illustrates the international recognition of the problem of nonadherence to immunosuppressive drugs.[1] It became clear, however, that with all the research that has been done we still know very little, especially about the risk-factors for nonadherence and effective interventions. It was recommended, among others, that future research projects should have a prospective and longitudinal design and outcome factors, clinical and economic, should be evaluated properly. A European initiative outside the transplantation field is the ABC-project, in which experts on the subject from several European institutes collaborate.[2] This newly started project is financed by the European Community, and the aim is to develop strategies for healthcare policy makers and healthcare providers, with the ambitious goal to enhance adherence in Europe. On a national level the joined collaboration of several Dutch institutes to enhance medication adherence through improvements in the Dutch healthcare system looks promising.[3] Two working conferences have been organized to date and several promising initiatives have been started.
Due to scarce evidence from mostly quantitative research results and regardless of the joined initiatives aiming at enhancement of adherence, in daily clinical practice we are still in need of adequate interventions that can help us in the case of the individual nonadherent patient. To obtain those interventions, useful information could also be provided by qualitative research. In daily practice we use a variety of interventions - in which endurance of the healthcare professional seems to be very important - in order to enhance the adherence of one individual patient. Regretfully desirable results can not always be observed by the healthcare professional. By simply asking the patient at a later time point in the treatment period what the healthcare professionals should or could have done to improve the patient's adherence the answer can also be surprisingly simple: "..*nothing, I just didn't want to change behaviour at that moment in my life.*".

The method described in Chapter 3 to measure nonadherence, electronic event monitoring, could well be used as an intervention tool in clinical practice. When patients face difficulties with taking their medication or when medication nonadherence is suspected, the medication taking behaviour could be assessed with electronic event monitoring (EEM). The main goal of using EEM – assessing and enhancing medication adherence - should be discussed openly with the patient as active collaboration is needed. During scheduled appointments in the hospital the downloaded information of the monitoring capsule can be discussed with the patient in a non-accusatory way. With the assistance of the healthcare professional more adequate medication taking behaviour could be obtained.

From Chapter 2, 6 en 7 it can be concluded that many publications concerning health-related quality of life of adult liver transplant patients report on results of a relatively short-term follow-up. As liver transplantation has been an accepted treatment option for several decades now, research on HRQOL and subjective side effects of immunosuppressive medication should focus also on the long-term survivors. More effort, by researchers, should be put into the development of a (liver) transplantation-specific instrument to assess HRQOL. This instrument should be used as a standard in research projects to allow a center-specific comparison.

In conclusion it is evident that ongoing research has to be performed with special emphasis on adherence and subjective patient reported outcomes. This allows us to improve the healthcare provided to the transplant recipient in a continuous way and to minimize the influence of the transplantation on the daily life of the patient.

REFERENCES

1. Fine RN, Becker Y, De Geest S, Eisen H, Ettenger R, Ewans R, Lapointe Rudow D, McKay D, Neu A, Nevins T, Reyes J, Wray J, Dobbels F. Nonadherence consensus conference summary report. Am J Transpl 2009;9:35-41.
2. Ascertaining barriers for compliance: policies for safe, effective and cost-effective use of medicines in Europe. www.abcproject.eu (accessed March 2009).
3. Westein MPD. Towards a better use of medicine. Recommendations to improve medicine adherence through improvements in the Dutch healthcare system. Abstract. Symposium European Society on Patient Adherence, Compliance and Persistence. September 5th 2008, Basel, Switzerland. www.therapietrouwbevorderen.nl

SAMENVATTING

Levertransplantatie is sinds tientallen jaren een behandelmogelijkheid voor patiënten met eindstadium leverziekte en voor een selecte groep van patiënten met erfelijke metabole afwijkingen. Sedert de beginjaren zijn de resultaten van levertransplantatie aanzienlijk verbeterd. Binnen al het wetenschappelijk onderzoek dat verricht is m.b.t. levertransplantatie heeft men betrekkelijk weinig aandacht geschonken aan de ervaringen van volwassen patiënten omtrent het leven met een levertransplantatie. Belangrijke samenhangende onderwerpen in dit opzicht zijn medicatieontrouw aan de medicijnen tegen afstoting, de subjectief ervaren bijwerkingen van de immuunsuppressiva (symptoomervaring) en de ervaren kwaliteit van leven op langere termijn.

Hoofdstuk 1 geeft een algemene inleiding over levertransplantatie en introduceert de drie onderwerpen van dit proefschrift, namelijk medicatieontrouw, subjectieve symptoomervaring en kwaliteit van leven op langere termijn.

In **Hoofdstuk 2** wordt een overzicht gepresenteerd van de bestaande literatuur over subjectieve symptoomervaring, medicatieontrouw en gezondheidsgerelateerde kwaliteit van leven op langere termijn na levertransplantatie van volwassen patiënten. Het werd duidelijk dat er - in tegenstelling tot bij patiënten na nier- en harttransplantatie - weinig onderzoek gedaan is naar de subjectieve symptoomervaring en medicatieontrouw van levertransplantatiepatiënten. Meer onderzoek is er verricht naar kwaliteit van leven. Zes onderzoeken zijn gevonden waarin subjectieve symptoomervaring werd beschreven in de onderzoeksmethodologie, meestal als onderdeel van een onderzoek naar kwaliteit van leven. Vastgesteld werd dat vrouwen meer symptoomongemak ten gevolge van de immuunsuppressiva hadden dan mannen.

In totaal 14 onderzoeken werden gevonden waarin de centrale doelstelling evaluatie van medicatieontrouw was. In het merendeel van deze studies werd medicatieontrouw onderzocht als onderdeel van een onderzoek naar het hervatten van alcohol en de onderzoeksmethoden van medicatieontrouw waren inadequaat. Medicatieontrouw van volwassen levertransplantatiepatiënten lijkt laag te zijn, maar als patiënten medicatieontrouw zijn dan kan er ernstige schade aangericht worden. Daarbij moet gedacht worden aan afstoting, verlies van de getransplanteerde lever of het overlijden van de patiënt. Beschreven risicofactoren voor medicatieontrouw zijn de kosten van medicijnen, een leeftijd jonger dan 40 jaar, psychische stoornissen, bijwerkingen van medicijnen, de gedachte dat medicijnen schadelijk zijn en de mate waarin de levertransplantatie een stempel drukt op het dagelijks leven van de patiënt.

Onderzoek naar gezondheidsgerelateerde kwaliteit van leven is meestal gericht geweest op de eerste maanden na levertransplantatie. In algemene zin kan vastgesteld worden dat de gezondheidsgerelateerde kwaliteit van leven als voldoende beoordeeld wordt door de patiënten, maar wel beneden het niveau van de 'gemiddelde Nederlander'. Over resultaten van gezondheidsgerelateerde kwaliteit van leven op langere termijn na levertransplantatie is nog weinig bekend.

De **hoofdstukken 3 tot en met 5** beschrijven onderzoeken die verricht zijn onder 123 volwassen levertransplantatiepatiënten.

In **hoofdstuk 3** wordt het resultaat van een onderzoek naar medicatieontrouw beschreven. Er zijn weinig onderzoeksgegevens bekend over de medicatietrouw van volwassen levertransplantatiepatiënten met betrekking tot de inname van de immuunsuppressiva. In ons onderzoek hebben wij in de thuissituatie de medicatietrouw met betrekking tot de inname van prednisolon prospectief bestudeerd met behulp van elektronische monitoring. Elektronische monitoring kan gedaan worden met een medicijnfles waarop een dop past met een ingebouwde microchip. De microchip registreert de datum en het tijdstip waarop de dop geopend en gesloten wordt. De mediaan van de '*taking compliance*' was 100% (range 60-105%), de mediaan van de '*dosing compliance*' was 99% (range 58-100%) en de mediaan van de '*timing compliance*' was 94% (42-100%). Een '*drug holiday*' van ≥ 48 uur werd gevonden bij 39% van de patiënten; van ≥ 72 uur bij 16% van de patiënten. Elektronische monitoring van de inname van prednisolon bij volwassen levertransplantatiepatiënten liet een hoog percentage medicatietrouw zien. De '*timing compliance*' was echter laag bij eenderde van de patiënten. Een leeftijd beneden de 40 bleek een belangrijke risicofactor te zijn voor een slechtere '*timing compliance*' en voor '*drug holidays*' van meer dan 48 uur.

Weinig onderzoeksgegevens zijn bekend over de invloed van medicatieontrouw op het klinisch resultaat. De doelstelling van het onderzoek dat gepresenteerd wordt in **Hoofdstuk 4** was om de invloed van medicatieontrouw met prednisolon, gemeten met elektronische monitoring, vast te kunnen stellen op het klinisch resultaat en de kosten van de gezondheidszorg gedurende een tijdsbestek van 2 jaar. Behoudens een iets hogere alkalische fosfatase bij patiënten met een lager percentage '*taking*' en '*dosing compliance*' en met meer '*drug holidays*' van ≥ 48 uur werd er geen relatie aangetoond tussen de verschillende definities van medicatietrouw en bloeduitslagen van de lever, acute afstoting, protocollaire verlaging van de medicijnen tegen afstoting, heropnames, en patiënt- en orgaanoverleving gedurende de 2 jaar van follow-up. Geconcludeerd kan worden dat de mate van medicatieontrouw met betrekking tot de inname van prednisolon dusdanig laag was dat het geen invloed heeft gehad op het klinisch resultaat. Dit is in tegenstelling tot resultaten van onderzoek onder nier- en harttransplantatiepatiënten waarbij een geringe mate van medicatieontrouw al geassocieerd kon worden met een slechter klinisch resultaat. Een mogelijke verklaring kan zijn dat de lever in immunologisch opzicht minder vatbaar is voor afstoting. Onderzoek in grotere patiëntengroepen kan wellicht duidelijk maken vanaf welk percentage van medicatieontrouw aan de immuunsuppressiva er een ongunstig effect op het klinisch resultaat van de levertransplantatie te bespeuren valt.

Symptoomervaring (vóórkomen en ervaren ongemak) verbonden aan bijwerkingen van immuunsuppressiva zou mogelijk een relatie kunnen hebben met medicatieontrouw en een slechtere kwaliteit van leven. De doelstellingen van het onderzoek dat gepresenteerd wordt in **Hoofdstuk 5** waren: primair, de symptoomervaring te schatten van klinisch stabiele volwassen patiënten gedurende langere termijn follow-up na levertransplantatie; secundair, het mogelijk verband te bestuderen tussen symptoomervaring en medicatieontrouw. Dit transversaal onderzoek omvatte 123 patiënt-

en. Symptoomervaring werd geschat met behulp van de 'Modified Transplant Symptom Occurrence and Symptom Distress Scale' (versie met 29 items) gedurende de jaarsevaluatie. Patiënten werden verdeeld in een cohort met een relatief korte tijdsduur na transplantatie (1-4 jaar) en een cohort met een langere tijdsduur na transplantatie (5-18 jaar). De resultaten toonden aan dat toegenomen haargroei de meest voorkomende bijwerking was bij mannen en vrouwen. Ervaren symptoomongemak was hoger bij vrouwen dan bij mannen. Het meeste ongemak hadden vrouwen ten gevolge van een heftige en pijnlijke menstruatie terwijl mannen het meeste ongemak ondervonden van impotentie. Duidelijke verschillen tussen symptoomvoorkomen en symptoomongemak werden zichtbaar tussen de groepen met een korte en lange tijdsduur na levertransplantatie en tussen mannen en vrouwen. Geen verband kon worden aangetoond tussen symptoomervaring en medicatieontrouw met prednisolon zoals het gemeten was met elektronische monitoring.

Hoofdstuk 6 en 7 gaat over onderzoeken naar de gezondheidstoestand van twee studiegroepen.

In 1979 werd de eerste levertransplantatie in ons ziekenhuis uitgevoerd. Wij waren geïnteresseerd in de huidige gezondheidstoestand van patiënten bij wie de levertransplantatie meer dan 15 jaar geleden was. Speciale interesse ging uit naar het brede scala van bijkomstige ziektes/co-morbiditeit en de ervaren levenskwaliteit door de patiënten. Resultaten worden gepresenteerd in **Hoofdstuk 6.** Alle patiënten die een levertransplantatie als volwassene ondergingen in de periode tussen maart 1979 en februari 1991, en die tenminste 15 jaar overleefd hadden kwamen in aanmerking voor het onderzoek. Co-morbiditeit bestaat overwegend uit overgewicht (57%), osteoporose (49%), maligniteiten (38%, voornamelijk huidkanker), hypertensie (38%), hart-en vaatziekten (19%), diabetes mellitus (22%), staar (24%), en een kreatinineklaring beneden 50 ml/min (11%). Acht patiënten (22%) ondergingen een retransplantatie, en gecompenseerde cirrose was aanwezig bij 4 patiënten (11%). Het patroon van co-morbiditeit leek gerelateerd te zijn aan de aard van de immuunsuppressiva welke voornamelijk bestonden uit prednisolon en azathioprine. Kwaliteit van leven werd ervaren als voldoende (7 op een schaal van 0-10). Desalniettemin rapporteerde ongeveer de helft van de patiënten beperkingen op het gebied van bewegen en dagelijkse activiteiten en pijn en ongemak. We kunnen vaststellen dat het resultaat van levertransplantatie in deze groep behoorlijk goed is. Verbeteringen kunnen o.a. bereikt worden door aanpassingen in de immuunsuppressiva.

Hoofdstuk 7 rapporteert de resultaten van een onderzoek naar gezondheidsgerelateerde kwaliteit van leven van patiënten die getransplanteerd werden vanwege familiaire amyloidotische polyneuropathie (FAP). FAP is een autosomaal dominant erfelijke afwijking geassocieerd met mutaties in het gen dat codeert voor het eiwit transthyretine, dat voornamelijk in de lever geproduceerd wordt. De karakteristieken van FAP zijn progressieve perifere en autonome neuropathie, maar ook amyloid afzetting in het hart komt vaak voor en kan het klinisch beeld overschaduwen. Aanvankelijk werd gerapporteerd dat levertransplantatie een algehele verbetering bewerkstelligde bij patiënten met FAP. Geleidelijk aan werd echter duidelijk dat in een belangrijk percentage van de patiënten voortgang van de ziekte in alle orgaansystemen niet

voorkomen kon worden. Inzicht in de gezondheidsgerelateerde kwaliteit van leven van getransplanteerde patiënten met FAP kan nuttig zijn om de geboden zorg aan deze patiëntengroep te verbeteren. Wij verrichtten een transversaal onderzoek om de gezondheidsgerelateerde kwaliteit van leven op langere termijn na levertransplantatie vast te kunnen stellen. Negen patiënten met een tijdsduur na levertransplantatie van 4 jaar of langer werden ingesloten. Ten tijde van de jaarlijkse controles werd de gezondheidsgerelateerde kwaliteit van leven gemeten met de Short Form-36 (SF-36). De resultaten werden vergeleken met patiënten die een levertransplantatie ondergingen vanwege een andere ziekte dan FAP en met de 'gemiddelde Nederlander'. Vóór de transplantatie hadden alle patiënten met FAP milde tot gemiddelde klachten van perifere polyneuropathie. De resultaten tonen aan dat de gezondheidsgerelateerde kwaliteit van leven in de eerste vier jaren na levertransplantatie stabiel bleef. Het domein van fysiek functioneren was 4 jaar na levertransplantatie significant lager vergeleken met niet-FAP getransplanteerde patiënten en de 'gemiddelde Nederlander'. Het domein van 'rolfunctioneren emotioneel' was vergelijkbaar met niet-FAP getransplanteerden en de controlegroep. Echter, op het merendeel van de domeinen scoorden de patiënten met FAP lager dan de niet-FAP getransplanteerden en de 'gemiddelde Nederlander'. Vanaf vier jaar na levertransplantatie lieten de drie patiënten met FAP met de langste overleving (9-12 jaar) verslechtering zien in alle domeinen, behalve op het gebied van zelfervaren geestelijke gezondheid. Deze studie, waarin slechts een klein aantal patiënten met FAP kon worden ingesloten, laat zien dat de gezondheidsgerelateerde kwaliteit van leven van deze patiënten na levertransplantatie relatief laag is en mogelijk verslechtert naarmate de tijdsduur na levertransplantatie langer is.

BLIK OP DE TOEKOMST

Kennis over de invloed van een levertransplantatie op het dagelijkse leven van de transplantatiepatiënt maakt het mogelijk dat gezondheidszorgmedewerkers de patiënten beter kunnen begeleiden en dat ze leren van de ervaringen van de patiënten.

Medicatieontrouw is in de afgelopen jaren een onderwerp van buitengewoon belang geworden, zowel internationaal als op landelijk niveau. De "Nonadherence Transplant Consensus Conference" in Tampa (USA, 2008) illustreert de internationale erkenning van o.a. het probleem van medicatieontrouw aan de medicijnen tegen afstoting, als onderdeel van therapietrouw.[1] Het werd ook duidelijk dat, ondanks al het onderzoek dat verricht is, wij nog steeds onvoldoende weten over de factoren die medicatieontrouw beïnvloeden, en over effectieve interventies. Eén van de aanbevelingen van de conferentie was dat toekomstige onderzoeksprojecten een prospectieve en longitudinale design moeten hebben waarbij klinische en economische eindpunten op juiste wijze onderzocht moeten worden. Een Europees initiatief buiten het aandachtsgebied van orgaantransplantatie is het ABC-project, waarin deskundigen vanuit diverse Europese instellingen samenwerken.[2] Dit project,

dat onlangs gestart is, wordt gesubsidieerd door de Europese Unie. Strategieën zullen ontwikkeld worden voor beleidsmakers op het gebied van de gezondheidszorg en voor gezondheidszorgmedewerkers met als belangrijk einddoel het verhogen van therapietrouw in Europa. Op nationaal niveau kan de samenwerking van diverse Nederlandse instituten om de medicatietrouw te verhogen door verbeteringen in het Nederlandse gezondheidszorgsysteem aan te brengen worden genoemd.[3] Twee werkconferenties werden georganiseerd en verschillende veelbelovende initiatieven zijn gestart.
Gelet op het schaarse bewijs dat grotendeels gebaseerd is op resultaten uit kwantitatief onderzoek en ondanks de vele gezamenlijke initiatieven om therapietrouw te verbeteren, wordt men in de dagelijkse praktijk gedwongen om zelf te zoeken naar effectieve interventies die kunnen helpen bij de individuele patiënt die medicatieontrouw is. Kwalitatief onderzoek, naast kwantitatief onderzoek, zou behulpzaam kunnen zijn om effectieve interventies te vinden. In de dagelijkse praktijk maken we gebruik van een breed scala aan interventies - waarbij het doorzettingsvermogen van de individuele medewerkers van groot belang blijkt te zijn – om de medicatietrouw van de individuele patiënt te verbeteren. Helaas blijven de gewenste resultaten vaak uit. Door de patiënt op een later moment in de tijd te vragen wat de medewerkers hadden kunnen doen om de medicatietrouw te verbeteren kan het antwoord verrassend eenvoudig zijn: "*...niets, ik was niet van plan om mijn gedrag op dat moment in mijn leven te veranderen*".

Elektronische meting (EM) van medicatietrouw zoals beschreven wordt in Hoofdstuk 3 zou gebruikt kunnen worden als middel om de medicatietrouw in de dagelijkse praktijk te verbeteren. Als patiënten moeilijkheden ondervinden met het innemen van hun medicijnen of wanneer medicatieontrouw wordt vermoed, dan zou het patroon van medicijngebruik met elektronische meting in kaart kunnen worden gebracht. Het belangrijkste doel van het toepassen van EM - inzicht krijgen in en het verbeteren van medicatietrouw – moet in alle openheid met de patiënt besproken worden omdat de volledige medewerking van de patiënt nodig is. Tijdens polikliniekbezoeken kan de opgeslagen informatie vanuit de microchip in de dop van de medicijnfles uitgelezen worden om vervolgens het innamepatroon in alle openheid met de patiënt te bespreken. Met hulp van de gezondheidszorgmedewerker zou op deze wijze een betere inname van de medicijnen bereikt kunnen worden.

Uit Hoofdstuk 2, 6 en 7 kan worden opgemaakt dat er veel gepubliceerd is over gezondheidsgerelateerde kwaliteit van leven van volwassen levertransplantatiepatiënten in de eerste jaren na de transplantatie. Aangezien levertransplantatie een behandeling is die al tientallen jaren zijn bestaansrecht heeft bewezen zou onderzoek naar gezondheidsgerelateerde kwaliteit van leven en subjectief ervaren bijwerkingen van immuunsuppressiva zich meer moeten richten op patiënten die al lang met de donorlever leven. Onderzoekers zouden zich meer moeten inspannen om een (lever) transplantatiespecifiek meetinstrument te ontwikkelen voor het meten van gezondheidsgerelateerde kwaliteit van leven. Dit meetinstrument zou gebruikt kunnen worden als standaard in onderzoeksprojecten waarbij óók een vergelijking

tussen verschillende centra gemaakt zou kunnen worden.
Samenvattend kan gesteld worden dat meer onderzoek nodig is met speciale nadruk op medicatietrouw en de ervaringen van de patiënten in het dagelijks leven. Dit onderzoek maakt het mogelijk om de zorg voor de transplantatiepatiënt steeds verder te verbeteren en om en negatieve invloed van de transplantatie op het dagelijkse leven van de patiënt te verminderen.

REFERENTIES

1. Fine RN, Becker Y, De Geest S, Eisen H, Ettenger R, Ewans R, Lapointe Rudow D, McKay D, Neu A, Nevins T, Reyes J, Wray J, Dobbels F. Nonadherence consensus conference summary report. Am J Transpl 2009;9:35-41.
2. Ascertaining barriers for compliance: policies for safe, effective and cost-effective use of medicines in Europe. www.ABCproject.eu (accessed March 2009).
3. Westein MPD. Towards a better use of medicine. Recommendations to improve medicine adherence through improvements in the Dutch healthcare system. Abstract. Symposium European Society on Patient Adherence, Compliance and Persistence. September 5th 2008, Basel, Switzerland. www.therapietrouwbevorderen.nl

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CURRICULUM VITAE

Gerda Drent werd geboren op 20 september 1956 in Bellingwedde. Haar jeugd bracht zij door in Oost-Groningen. In 1974 behaalde zij haar Atheneumdiploma aan de Rijksscholengemeenschap in Ter-Apel. Aanvankelijk startte zij een studie Scandinavische Taal- en Letterkunde, met de Noorse taal als hoofdvak, maar na zo'n 2 jaar besloot zij over te stappen naar de gezondheidszorg. In eerste instantie was zij werkzaam als gediplomeerd doktersassistente bij het Huisartsenlaboratorium in Groningen, maar in 1979, vanuit een functie als ECG-laborante in het Academisch Ziekenhuis te Groningen, begon zij met de inservice-opleiding tot verpleegkundige in datzelfde ziekenhuis. Na haar diplomering volgden nog de Intensive Care opleiding en de Midden Management Opleiding. Werkervaring deed zij op bij de afdeling Chirurgie, daar verpleegde zij onder andere levertransplantatiepatiënten die complicaties kregen na de transplantatie, en daarna volgden de Coronary Care Unit en de afdeling Spoedeisende Hulp Interne Geneeskunde. De Spoedeisende Hulp zorgde ondermeer voor de eerste opvang van lever(transplantatie)patiënten met problemen als koorts en bloedingen uit slokdarmspataderen.
In 1991 kreeg zij de functie van Verpleegkundig Specialist Levertransplantatie bij de volwassen patiënten. Een 4-jarige deeltijdstudie Verplegingswetenschap aan de Universiteit van Maastricht (MUG-verband (Maastricht, Utrecht, Groningen)) werd opgepakt in 1995 en eind 1999 kon de bul in ontvangst genomen worden. Tijdens deze studie werd een start gemaakt met het onderzoek naar de medicatietrouw van levertransplantatiepatiënten.
Gerda Drent heeft aan de wieg gestaan van de ontwikkeling van de transplantatieverpleegkunde in Nederland. Zij was mede-initiatiefneemster van de Werkgroep Transplantatieverpleegkunde UMCG (WTV), de Landelijke Werkgroep Transplantatieverpleegkundigen (LWTV) en van de vervolgopleiding Transplantatieverpleegkunde.